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(71) Applicant (for all designated States except US): ELAN PHARMACEUTICALS, INC. [US/US]; 800 Gateway Boulevard, South San Francisco, Ca 94080 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): GAILUNAS, Andrea [US/US]; 1105 Baywater Avenue, Apartment #1, Burlingame, CA 94010 (US). TUCKER, John, Alan [US/US]; 37 Creekridge Court, San Mateo, CA 94402 (US). JOHN, Varghese [US/US]; 1722 18th Avenue, San Francisco, CA 94122 (US).

(74) Agent: SARUSSI, Steven, J.; McDonnell Boehnen Hulbert & Berghoff, Suite 3200, 300 South Wacker Drive, Chicago, IL 60606 (US).

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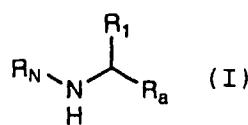
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(54) Title: SUBSTITUTED AMINES FOR THE TREATMENT OF ALZHEIMER'S DISEASE



(57) Abstract: Disclosed are compounds of formula (I) which are useful in treating Alzheimer's disease and other similar diseases. These compounds include inhibitors of the beta-secretase enzyme that are useful in the treatment of Alzheimer's disease and other diseases characterized by deposition of A beta peptide in a mammal. The compounds of the invention are useful in pharmaceutical compositions and methods of treatment to reduce A beta peptide formation.

**SUBSTITUTED AMINES FOR
THE TREATMENT OF ALZHEIMER'S DISEASE**

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority from U.S. Provisional
5 Application Serial Number 60/324,407, filed September 24, 2001,
the disclosure of which is incorporated herein by reference in
its entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

10 The invention relates to substituted amines and to such
compounds that are useful in the treatment of Alzheimer's
disease and related diseases. More specifically, it relates to
such compounds that are capable of inhibiting beta-secretase,
an enzyme that cleaves amyloid precursor protein to produce
15 amyloid beta peptide (A beta), a major component of the amyloid
plaques found in the brains of Alzheimer's sufferers.

Background of the Invention

Alzheimer's disease (AD) is a progressive degenerative
disease of the brain primarily associated with aging. Clinical
20 presentation of AD is characterized by loss of memory,
cognition, reasoning, judgment, and orientation. As the
disease progresses, motor, sensory, and linguistic abilities
are also affected until there is global impairment of multiple
cognitive functions. These cognitive losses occur gradually,
25 but typically lead to severe impairment and eventual death in
the range of four to twelve years.

Alzheimer's disease is characterized by two major
pathologic observations in the brain: neurofibrillary tangles
and beta amyloid (or neuritic) plaques, comprised predominantly
30 of an aggregate of a peptide fragment know as A beta.
Individuals with AD exhibit characteristic beta-amyloid
deposits in the brain (beta amyloid plaques) and in cerebral
blood vessels (beta amyloid angiopathy) as well as
neurofibrillary tangles. Neurofibrillary tangles occur not

only in Alzheimer's disease but also in other dementia-inducing disorders. On autopsy, large numbers of these lesions are generally found in areas of the human brain important for memory and cognition.

5 Smaller numbers of these lesions in a more restricted anatomical distribution are found in the brains of most aged humans who do not have clinical AD. Amyloidogenic plaques and vascular amyloid angiopathy also characterize the brains of individuals with Trisomy 21 (Down's Syndrome), Hereditary
10 Cerebral Hemorrhage with Amyloidosis of the Dutch-Type (HCHWA-D), and other neurodegenerative disorders. Beta-amyloid is a defining feature of AD, now believed to be a causative precursor or factor in the development of disease. Deposition of A beta in areas of the brain responsible for cognitive
15 activities is a major factor in the development of AD. Beta-amyloid plaques are predominantly composed of amyloid beta peptide (A beta, also sometimes designated betaA4). A beta peptide is derived by proteolysis of the amyloid precursor protein (APP) and is comprised of 39-42 amino acids. Several
20 proteases called secretases are involved in the processing of APP.

25 Cleavage of APP at the N-terminus of the A beta peptide by beta-secretase and at the C-terminus by one or more gamma-secretases constitutes the beta-amyloidogenic pathway, i.e. the pathway by which A beta is formed. Cleavage of APP by alpha-secretase produces alpha-sAPP, a secreted form of APP that does not result in beta-amyloid plaque formation. This alternate pathway precludes the formation of A beta peptide. A description of the proteolytic processing fragments of APP is
30 found, for example, in U.S. Patent Nos. 5,441,870; 5,721,130; and 5,942,400.

35 An aspartyl protease has been identified as the enzyme responsible for processing of APP at the beta-secretase cleavage site. The beta-secretase enzyme has been disclosed using varied nomenclature, including BACE, Asp, and Memapsin.

See, for example, Sinha et al., 1999, *Nature* 402:537-554 (p501) and published PCT application WO00/17369.

Several lines of evidence indicate that progressive cerebral deposition of beta-amyloid peptide (A beta) plays a 5 seminal role in the pathogenesis of AD and can precede cognitive symptoms by years or decades. See, for example, Selkoe, 1991, *Neuron* 6:487. Release of A beta from neuronal cells grown in culture and the presence of A beta in cerebrospinal fluid (CSF) of both normal individuals and AD 10 patients has been demonstrated. See, for example, Seubert et al., 1992, *Nature* 359:325-327.

It has been proposed that A beta peptide accumulates as a result of APP processing by beta-secretase, thus inhibition of this enzyme's activity is desirable for the treatment of AD. 15 In vivo processing of APP at the beta-secretase cleavage site is thought to be a rate-limiting step in A beta production, and is thus a therapeutic target for the treatment of AD. See for example, Sabbagh, M., et al., 1997, *Alz. Dis. Rev.* 3, 1-19.

BACE1 knockout mice fail to produce A beta, and present a 20 normal phenotype. When crossed with transgenic mice that over express APP, the progeny show reduced amounts of A beta in brain extracts as compared with control animals (Luo et al., 2001 *Nature Neuroscience* 4:231-232). This evidence further supports the proposal that inhibition of beta-secretase 25 activity and reduction of A beta in the brain provides a therapeutic method for the treatment of AD and other beta amyloid disorders.

At present there are no effective treatments for halting, preventing, or reversing the progression of Alzheimer's 30 disease. Therefore, there is an urgent need for pharmaceutical agents capable of slowing the progression of Alzheimer's disease and/or preventing it in the first place.

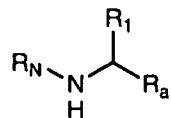
Compounds that are effective inhibitors of beta-secretase, that inhibit beta-secretase-mediated cleavage of APP, that are 35 effective inhibitors of A beta production, and/or are effective

to reduce amyloid beta deposits or plaques, are needed for the treatment and prevention of disease characterized by amyloid beta deposits or plaques, such as AD.

SUMMARY OF THE INVENTION

The invention encompasses the compounds of formula (I) shown below, pharmaceutical compositions containing the 5 compounds and methods employing such compounds or compositions in the treatment of Alzheimer's disease and more specifically compounds that are capable of inhibiting beta-secretase, an enzyme that cleaves amyloid precursor protein to produce A-beta peptide, a major component of the amyloid plaques found in the 10 brains of Alzheimer's sufferers.

In one aspect, the invention provides compounds of the formula I:



(I)

15

and pharmaceutically acceptable salts thereof, wherein

R_1 is $-(\text{CH}_2)_{1-2}-\text{S}(\text{O})_{0-2}-(\text{C}_1-\text{C}_6$ alkyl), or

C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 groups 20 independently selected from halogen, -OH, =O, -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino, -N(R)C(O)R'-, -OC(=O)-amino and -OC(=O)-mono- or dialkylamino, or

C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally 25 substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, and mono- or dialkylamino, or

aryl, heteroaryl, heterocyclyl, aryl-(C₁-C₆)alkyl-, heteroaryl-(C₁-C₆)alkyl-, or heterocyclyl-(C₁-C₆)alkyl-, where the ring portions of each are 30 optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, -OH, -SH, -C≡N, -NO₂, -NR₁₀₅R'₁₀₅, -CO₂R, -N(R)COR', -N(R)SO₂R',

-C(=O)-(C₁-C₄) alkyl, -SO₂-amino, -SO₂-monoalkylamino,
-SO₂-dialkylamino, -C(=O)-amino, -C(=O)-
monoalkylamino, -C(=O)-dialkylamino, -SO₂-(C₁-C₄)
alkyl,

5 C₁-C₆ alkoxy optionally substituted with 1, 2, or 3
groups which are independently selected from
halogen,

10 C₃-C₇ cycloalkyl optionally substituted with 1, 2, or
3 groups independently selected from halogen, -
OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, -C₁-C₆
alkyl and mono- or dialkylamino,

15 C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3
groups independently selected from halogen, -OH,
-SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or
dialkylamino and -C₁-C₃ alkyl, and

20 C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl each of which is
optionally substituted with 1, 2, or 3 groups
independently selected from halogen, -OH, -SH,
-C≡N, -CF₃, C₁-C₃ alkoxy, amino, C₁-C₆ alkyl and
mono- or dialkylamino; and the heterocyclyl
group is optionally further substituted with
oxo;

R and R' independently are hydrogen, C₁-C₁₀ alkyl, C₁-C₁₀
alkylaryl or C₁-C₁₀ alkylheteroaryl;

25 R_N is R'₁₀₀, -SO₂R'₁₀₀, -(CRR')₁₋₆R'₁₀₀, -C(=O)-(CRR')₀₋₆R₁₀₀, -C(=O)-
(CRR')₁₋₆-O-R'₁₀₀, -C(=O)-(CRR')₁₋₆-S-R'₁₀₀, -C(=O)-(CRR')₁₋₆-
C(=O)-R₁₀₀, -C(=O)-(CRR')₁₋₆-SO₂-R₁₀₀ or -C(=O)-(CRR')₁₋₆-
NR₁₀₀-R'₁₀₀;

30 R₁₀₀ and R'₁₀₀ independently represent aryl, heteroaryl,
heterocyclyl, -aryl-W-aryl, -aryl-W-heteroaryl, -aryl-W-
heterocyclyl, -heteroaryl-W-aryl, -heteroaryl-W-
heteroaryl, -heteroaryl-W- heterocyclyl, -heterocyclyl-W-
aryl, -heterocyclyl-W-heteroaryl, -heterocyclyl-W-
heterocyclyl, -CH[(CH₂)₀₋₂-O-R₁₅₀]-(CH₂)₀₋₂-aryl, -CH[(CH₂)₀₋₂-
O-R₁₅₀]-(CH₂)₀₋₂-heterocyclyl or -CH[(CH₂)₀₋₂-O-R₁₅₀]-(CH₂)₀₋₂-

heteroaryl, where the ring portions of each are optionally substituted with 1, 2, or 3 groups independently selected from

-OR, -NO₂, C₁-C₆ alkyl, halogen, -C≡N, -OCF₃, -CF₃, -(CH₂)₀₋₄-O-P(=O)(OR)(OR'), -(CH₂)₀₋₄-CO-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-O-(CH₂)₀₋₄-CONR₁₀₂R'₁₀₂, -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl), -(CH₂)₀₋₄-CO-(CH₂)₀₋₄(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-R₁₁₀, -(CH₂)₀₋₄-R₁₂₀, -(CH₂)₀₋₄-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₁₀, -(CH₂)₀₋₄-CO-R₁₂₀, -(CH₂)₀₋₄-CO-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₄₀, -(CH₂)₀₋₄-CO-O-R₁₅₀, -(CH₂)₀₋₄-SO₂-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-SO-(C₁-C₈ alkyl), -(CH₂)₀₋₄-SO₂-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-SO₂-(CH₂)₀₋₄(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-N(R₁₅₀)-CO-O-R₁₅₀, -(CH₂)₀₋₄-N(R₁₅₀)-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CS-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CO-R₁₀₅, -(CH₂)₀₋₄-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-R₁₄₀, -(CH₂)₀₋₄-O-CO-(C₁-C₆ alkyl), -(CH₂)₀₋₄-O-P(O)-(O-R₁₁₀)₂, -(CH₂)₀₋₄-O-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-O-CS-N(R₁₅₀)₂, -(CH₂)₀₋₄-O-(R₁₅₀), -(CH₂)₀₋₄-O-R₁₅₀'-COOH, -(CH₂)₀₋₄-S-(R₁₅₀), -(CH₂)₀₋₄-N(R₁₅₀)-SO₂-R₁₀₅, -(CH₂)₀₋₄(C₃-C₇ cycloalkyl), (C₂-C₁₀) alkenyl, and (C₂-C₁₀) alkynyl, or

R₁₀₀ is C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 R₁₁₅ groups, or

R₁₀₀ is -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl) or -(C₁-C₆ alkyl)-S-(C₁-C₆ alkyl), each of which is optionally substituted with 1, 2, or 3 R₁₁₅ groups, or

R₁₀₀ is C₃-C₈ cycloalkyl optionally substituted with 1, 2, or 3 R₁₁₅ groups;

W is -(CH₂)₀₋₄-, -O-, -S(O)₀₋₂-, -N(R₁₃₅)-, -CR(OH)- or -C(O)-;

R₁₀₂ and R₁₀₂' independently are hydrogen, or

C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, aryl or -R₁₁₀;

R₁₀₅ and R'₁₀₅ independently represent -H, -R₁₁₀, -R₁₂₀, C₃-C₇ cycloalkyl, -(C₁-C₂ alkyl)-(C₃-C₇ cycloalkyl), -(C₁-C₆ alkyl)-O-(C₁-C₃ alkyl), C₂-C₆ alkenyl, C₂-C₆ alkynyl, or C₁-

C₆ alkyl chain with one double bond and one triple bond,
or
C₁-C₆ alkyl optionally substituted with -OH or -NH₂; or,
C₁-C₆ alkyl optionally substituted with 1, 2, or 3 groups
5 independently selected from halogen, or
R₁₀₅ and R'₁₀₅ together with the atom to which they are attached
form a 3 to 7 membered carbocyclic ring, where one member
is optionally a heteratom selected from -O-, -S(O)₀₋₂₋, -
N(R₁₃₅)-, the ring being optionally substituted with 1, 2
10 or 3 independently selected R₁₄₀ groups;
R₁₁₅ at each occurrence is independently halogen, -OH, -CO₂R₁₀₂,
-C₁-C₆ thioalkoxy, -CO₂-phenyl, -NR₁₀₅R'₁₃₅, -SO₂-(C₁-C₈
alkyl), -C(=O)R₁₈₀, R₁₈₀, -CONR₁₀₅R'₁₀₅, -SO₂NR₁₀₅R'₁₀₅, -NH-CO-
15 (C₁-C₆ alkyl), -NH-C(=O)-OH, -NH-C(=O)-OR, -NH-C(=O)-O-
phenyl, -O-C(=O)-(C₁-C₆ alkyl), -O-C(=O)-amino, -O-C(=O)-
mono- or dialkylamino, -O-C(=O)-phenyl, -O-(C₁-C₆ alkyl)-
CO₂H, -NH-SO₂-(C₁-C₆ alkyl), C₁-C₆ alkoxy or C₁-C₆
haloalkoxy;
R₁₃₅ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇
20 cycloalkyl, -(CH₂)₀₋₂₋(aryl), -(CH₂)₀₋₂₋(heteroaryl), or -(CH₂)₀₋₂₋(heterocyclyl);
R₁₄₀ is heterocyclyl optionally substituted with 1, 2, 3, or 4
groups independently selected from C₁-C₆ alkyl, C₁-C₆
25 alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C₁-
C₆)alkylamino, di(C₁-C₆)alkylamino, C₂-C₆ alkenyl, C₂-C₆
alkynyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, amino(C₁-
C₆)alkyl, mono(C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-
C₆)alkylamino(C₁-C₆)alkyl, and =O;
R₁₅₀ is hydrogen, C₃-C₇ cycloalkyl, -(C₁-C₂ alkyl)-(C₃-C₇
30 cycloalkyl), C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkyl with
one double bond and one triple bond, -R₁₁₀, -R₁₂₀, or
C₁-C₆ alkyl optionally substituted with 1, 2, 3, or 4
groups independently selected from -OH, -NH₂, C₁-C₃
alkoxy, R₁₁₀, and halogen;

R_{150'} is C₃-C₇ cycloalkyl, -(C₁-C₃ alkyl)-(C₃-C₇ cycloalkyl), C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkyl with one double bond and one triple bond, -R₁₁₀, -R₁₂₀, or C₁-C₆ alkyl optionally substituted with 1, 2, 3, or 4 groups independently selected from -OH, -NH₂, C₁-C₃ alkoxy, R₁₁₀, and halogen;

R₁₈₀ is selected from morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S-oxide, homothiomorpholinyl S,S-dioxide, pyrrolinyl and pyrrolidinyl, each of which is optionally substituted with 1, 2, 3, or 4 groups independently selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, amino(C₁-C₆)alkyl, mono(C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl, and =O;

R₁₁₀ is aryl optionally substituted with 1 or 2 R₁₂₅ groups;

R₁₂₅ at each occurrence is independently halogen, amino, mono- or dialkylamino, -OH, -C≡N, -SO₂-NH₂, -SO₂-NH-C₁-C₆ alkyl, -SO₂-N(C₁-C₆ alkyl)₂, -SO₂-(C₁-C₄ alkyl), -CO-NH₂, -CO-NH-C₁-C₆ alkyl, or -CO-N(C₁-C₆ alkyl)₂, or C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently selected from C₁-C₃ alkyl, halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, and mono- and dialkylamino, or

C₁-C₆ alkoxy optionally substituted with one, two or three of halogen;

R₁₂₀ is heteroaryl, which is optionally substituted with 1 or 2 R₁₂₅ groups; and

R₁₃₀ is heterocyclyl optionally substituted with 1 or 2 R₁₂₅ groups; and

R_a represents hydrogen, hydroxymethyl, or -CH(OH)CH₂CH₂R₂, wherein R₂ is R₁₂₀ or R₁₃₀.

The invention also provides methods for the treatment or prevention of Alzheimer's disease, mild cognitive impairment Down's syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, cerebral amyloid angiopathy, 5 other degenerative dementias, dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease comprising 10 administration of a therapeutically effective amount of a compound or salt of formula I, to a patient in need thereof.

Preferably, the patient is a human.

More preferably, the disease is Alzheimer's disease.

More preferably, the disease is dementia.

15 The invention also provides pharmaceutical compositions comprising a compound or salt of formula I and at least one pharmaceutically acceptable carrier, solvent, adjuvant or diluent.

20 The invention also provides the use of a compound or salt according to formula I for the manufacture of a medicament.

The invention also provides the use of a compound or salt of formula I for the treatment or prevention of Alzheimer's disease, mild cognitive impairment Down's syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, 25 cerebral amyloid angiopathy, other degenerative dementias, dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, or diffuse Lewy body type of 30 Alzheimer's disease.

The invention also provides compounds, pharmaceutical compositions, kits, and methods for inhibiting beta-secretase-mediated cleavage of amyloid precursor protein (APP). More particularly, the compounds, compositions, and methods of the 35 invention are effective to inhibit the production of A-beta

peptide and to treat or prevent any human or veterinary disease or condition associated with a pathological form of A-beta peptide.

The compounds, compositions, and methods of the invention
5 are useful for treating humans who have Alzheimer's Disease (AD), for helping prevent or delay the onset of AD, for treating patients with mild cognitive impairment (MCI), and preventing or delaying the onset of AD in those patients who would otherwise be expected to progress from MCI to AD, for
10 treating Down's syndrome, for treating Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch Type, for treating cerebral beta-amyloid angiopathy and preventing its potential consequences such as single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias
15 of mixed vascular and degenerative origin, for treating dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, and diffuse Lewy body type AD, and for treating frontotemporal dementias with
20 parkinsonism (FTDP).

The compounds of the invention possess beta-secretase inhibitory activity. The inhibitory activities of the compounds of the invention is readily demonstrated, for example, using one or more of the assays described herein or
25 known in the art.

Unless the substituents for a particular formula are expressly defined for that formula, they are understood to carry the definitions set forth in connection with the preceding formula to which the particular formula makes
30 reference.

The invention also provides methods of preparing the compounds of the invention and the intermediates used in those methods.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the invention provides compounds of formula I.

Preferred compounds of formula I include those of formula I-1, i.e., compounds of formula I wherein

5 R_1 is aryl, heteroaryl, heterocyclyl, aryl-(C₁-C₆)alkyl-, heteroaryl-(C₁-C₆)alkyl-, or heterocyclyl-(C₁-C₆)alkyl-, where the ring portions of each are optionally substituted with 1, 2, 3, or 4 groups

10 independently selected from halogen, -OH, -SH, -C≡N, -NO₂, -NR₁₀₅R'₁₀₅, -CO₂R, -N(R)COR', or -N(R)SO₂R', -C(=O)-(C₁-C₄) alkyl, -SO₂-amino, -SO₂-mono or dialkylamino, -C(=O)-amino, -C(=O)-mono or dialkylamino, -SO₂-(C₁-C₄) alkyl, or

15 C₁-C₆ alkoxy optionally substituted with 1, 2, or 3 groups which are independently selected from halogen, or

20 C₃-C₇ cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, -C₁-C₆ alkyl and mono- or dialkylamino, or

25 C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino and -C₁-C₃ alkyl, or

30 C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, C₁-C₆ alkyl and mono- or dialkylamino; and the heterocyclyl group is optionally further substituted with oxo.

Preferred compounds of formula I-1 also include those wherein

R₁ is aryl-(C₁-C₆)alkyl-, heteroaryl-(C₁-C₆)alkyl-, or heterocyclyl-(C₁-C₆)alkyl-, where the ring portions of each are optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, -OH, -SH, 5 -C≡N, -NO₂, -NR₁₀₅R'₁₀₅, -CO₂R, -N(R)COR', or -N(R)SO₂R', -C(=O)-(C₁-C₄) alkyl, -SO₂-amino, -SO₂-mono or dialkylamino, -C(=O)-amino, -C(=O)-mono or dialkylamino, -SO₂-(C₁-C₄) alkyl, or 10 C₁-C₆ alkoxy optionally substituted with 1, 2, or 3 groups which are independently selected from halogen, or C₃-C₇ cycloalkyl optionally substituted with 1, 2, or 15 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, -C₁-C₆ alkyl and mono- or dialkylamino, or C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino and -C₁-C₃ alkyl, or 20 C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, C₁-C₆ alkyl and mono- or dialkylamino; and the heterocyclyl 25 group is optionally further substituted with oxo.

Preferred compounds of formula I-1 also include those wherein

R₁ is -(CH₂)-aryl, -(CH₂)-heteroaryl, or -(CH₂)-heterocyclyl, 30 where the ring portions of each are optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, -OH, -SH, -C≡N, -NO₂, -NR₁₀₅R'₁₀₅, -CO₂R, -N(R)COR', or -N(R)SO₂R', -C(=O)-(C₁-C₄) alkyl, -SO₂-amino, -SO₂-mono or

dialkylamino, $-\text{C}(=\text{O})-\text{amino}$, $-\text{C}(=\text{O})-\text{mono}$ or
dialkylamino, $-\text{SO}_2-(\text{C}_1-\text{C}_4)$ alkyl, or
C₁-C₆ alkoxy optionally substituted with 1, 2, or 3
groups which are independently selected from
5 halogen, or
C₃-C₇ cycloalkyl optionally substituted with 1, 2, or
3 groups independently selected from halogen, -
OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, -C₁-C₆
alkyl and mono- or dialkylamino, or
10 C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3
groups independently selected from halogen, -OH,
-SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or
dialkylamino and -C₁-C₃ alkyl, or.
15 C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl each of which is
optionally substituted with 1, 2, or 3 groups
independently selected from halogen, -OH, -SH,
-C≡N, -CF₃, C₁-C₃ alkoxy, amino, C₁-C₆ alkyl and
mono- or dialkylamino; and the heterocyclyl
group is optionally further substituted with
20 oxo.

Preferred compounds of formula I-1 also include those
wherein
R₁ is -CH₂-phenyl or -CH₂-pyridinyl where the ring portions of
each are optionally substituted with 1, 2, 3, or 4 groups
25 independently selected from halogen, C₁-C₄ alkoxy,
hydroxy, -NO₂, and
C₁-C₄ alkyl optionally substituted with 1, 2, or 3
substituents independently selected from halogen, OH,
SH, NH₂, NH(C₁-C₆ alkyl), N-(C₁-C₆ alkyl)(C₁-C₆ alkyl),
30 C≡N, CF₃.

Preferred compounds of formula I-1 also include those
wherein
R₁ is -CH₂-phenyl or -CH₂-pyridinyl where the phenyl or
pyridinyl rings are each optionally substituted with 1 or

2 groups independently selected from halogen, C₁-C₂ alkyl, C₁-C₂ alkoxy, hydroxy, -CF₃, and -NO₂.

Preferred compounds of formula I-2 include those wherein R₁ is -CH₂-phenyl or -CH₂-pyridinyl where the phenyl or 5 pyridinyl rings are each optionally substituted with 2 groups independently selected from halogen, C₁-C₂ alkyl, C₁-C₂ alkoxy, hydroxy, and -NO₂.

Preferred compounds of formula I-1 also include those wherein R₁ is -CH₂-pyridinyl, benzyl, 3,5-difluorobenzyl, or 5-10 hydroxybenzyl.

Preferred compounds of formula I and I-1 include compounds of formula I-2, i.e., those of formula I or formula I-1, wherein

R_N is -C(=O)-(CRR')₀₋₆R₁₀₀;

15 R₁₀₀ represents aryl, heteroaryl, heterocyclyl, -aryl-W-aryl, -aryl-W-heteroaryl, -aryl-W-heterocyclyl, -heteroaryl-W-aryl, -heteroaryl-W-heteroaryl, -heteroaryl-W-heterocyclyl, -heterocyclyl-W-heteroaryl, -heterocyclyl-W-heterocyclyl, -CH[(CH₂)₀₋₂-O-R₁₅₀]- (CH₂)₀₋₂-aryl, -CH[(CH₂)₀₋₂-O-R₁₅₀]- (CH₂)₀₋₂-heterocyclyl 20 or -CH[(CH₂)₀₋₂-O-R₁₅₀]- (CH₂)₀₋₂-heteroaryl, where the ring portions of each are optionally substituted with 1, 2, or 3 groups independently selected from

-OR, -NO₂, C₁-C₆ alkyl, halogen, -C≡N, -OCF₃, -CF₃, -(CH₂)₀₋₄-O-P(=O)(OR)(OR'), -(CH₂)₀₋₄-CO-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-O-(CH₂)₀₋₄-CONR₁₀₂R₁₀₂', -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl), -(CH₂)₀₋₄-CO-(CH₂)₀₋₄(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-R₁₁₀, -(CH₂)₀₋₄-R₁₂₀, -(CH₂)₀₋₄-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₁₀, -(CH₂)₀₋₄-CO-R₁₂₀, -(CH₂)₀₋₄-CO-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₄₀, -(CH₂)₀₋₄-CO-O-R₁₅₀, -(CH₂)₀₋₄-SO₂-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-SO-(C₁-C₈ 30 alkyl), -(CH₂)₀₋₄-SO₂-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-SO₂-(CH₂)₀₋₄(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-N(R₁₅₀)-CO-O-R₁₅₀, -(CH₂)₀₋₄-N(R₁₅₀)-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)₂-CS-35 N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CO-R₁₀₅, -(CH₂)₀₋₄-NR₁₀₅R'₁₀₅,

- $(\text{CH}_2)_{0-4}-\text{R}_{140}$, - $(\text{CH}_2)_{0-4}-\text{O}-\text{CO}-\text{(C}_1\text{-C}_6\text{ alkyl)}$, - $(\text{CH}_2)_{0-4}-\text{O}-\text{P(O)}-\text{(O-R}_{110}\text{)}_2$, - $(\text{CH}_2)_{0-4}-\text{O}-\text{CO-N(R}_{150}\text{)}_2$, - $(\text{CH}_2)_{0-4}-\text{O}-\text{CS-N(R}_{150}\text{)}_2$, - $(\text{CH}_2)_{0-4}-\text{O-}(R_{150})$, - $(\text{CH}_2)_{0-4}-\text{O-R}_{150}'-\text{COOH}$, - $(\text{CH}_2)_{0-4}-\text{S-}(R_{150})$, - $(\text{CH}_2)_{0-4}-\text{N(R}_{150}\text{)}-\text{SO}_2\text{-R}_{105}$, - $(\text{CH}_2)_{0-4}-\text{C}_3\text{-C}_7\text{ cycloalkyl}$, $(\text{C}_2\text{-C}_{10})$ alkenyl, or $(\text{C}_2\text{-C}_{10})$ alkynyl,
5 or

R_{100} is $\text{C}_1\text{-C}_{10}$ alkyl optionally substituted with 1, 2, or 3 R_{115} groups, or

10 R_{100} is $-(\text{C}_1\text{-C}_6\text{ alkyl})-\text{O-C}_1\text{-C}_6\text{ alkyl}$ or $-(\text{C}_1\text{-C}_6\text{ alkyl})-\text{S-}(\text{C}_1\text{-C}_6\text{ alkyl})$, each of which is optionally substituted with 1, 2, or 3 R_{115} groups, or

R_{100} is $\text{C}_3\text{-C}_8$ cycloalkyl optionally substituted with 1, 2, or 3 R_{115} groups.

15 Preferred compounds of formula I-2 include compounds wherein

R_N is $-\text{C}(=\text{O})-(\text{CRR}')_{0-6}\text{R}_{100}$; and

R_{100} represents aryl, heteroaryl, or heterocyclyl, where the ring portions of each are optionally substituted with 1, 2, or 3 groups independently selected from

20 -OR, -NO₂, C₁-C₆ alkyl, halogen, -C≡N, -OCF₃, -CF₃, - $(\text{CH}_2)_{0-4}-\text{O-P(O)(OR)(OR')}$, - $(\text{CH}_2)_{0-4}-\text{CO-NR}_{105}\text{R}'_{105}$, - $(\text{CH}_2)_{0-4}-\text{O-(CH}_2)_{0-4}-\text{CONR}_{102}\text{R}_{102}'$, - $(\text{CH}_2)_{0-4}-\text{CO-}(\text{C}_1\text{-C}_{12}\text{ alkyl})$, - $(\text{CH}_2)_{0-4}-\text{CO-}(\text{C}_2\text{-C}_{12}\text{ alkenyl})$, - $(\text{CH}_2)_{0-4}-\text{CO-}(\text{C}_2\text{-C}_{12}\text{ alkynyl})$, - $(\text{CH}_2)_{0-4}-\text{CO-}(\text{CH}_2)_{0-4}(\text{C}_3\text{-C}_7\text{ cycloalkyl})$, - $(\text{CH}_2)_{0-4}-\text{R}_{110}$, - $(\text{CH}_2)_{0-4}-\text{R}_{120}$, - $(\text{CH}_2)_{0-4}-\text{R}_{130}$, - $(\text{CH}_2)_{0-4}-\text{CO-R}_{110}$, - $(\text{CH}_2)_{0-4}-\text{CO-R}_{120}$, - $(\text{CH}_2)_{0-4}-\text{CO-R}_{130}$, - $(\text{CH}_2)_{0-4}-\text{CO-R}_{140}$, - $(\text{CH}_2)_{0-4}-\text{CO-O-R}_{150}$, - $(\text{CH}_2)_{0-4}-\text{SO}_2\text{-NR}_{105}\text{R}'_{105}$, - $(\text{CH}_2)_{0-4}-\text{SO-}(\text{C}_1\text{-C}_8\text{ alkyl})$, - $(\text{CH}_2)_{0-4}-\text{SO}_2\text{-}(\text{C}_1\text{-C}_{12}\text{ alkyl})$, - $(\text{CH}_2)_{0-4}-\text{SO}_2\text{-}(\text{CH}_2)_{0-4}(\text{C}_3\text{-C}_7\text{ cycloalkyl})$, - $(\text{CH}_2)_{0-4}-\text{N(R}_{150}\text{)}-\text{CO-O-R}_{150}$, - $(\text{CH}_2)_{0-4}-\text{N(R}_{150}\text{)}-\text{CO-N(R}_{150}\text{)}_2$, - $(\text{CH}_2)_{0-4}-\text{N(R}_{150}\text{)}-\text{CS-N(R}_{150}\text{)}_2$, - $(\text{CH}_2)_{0-4}-\text{N(R}_{150}\text{)}-\text{CO-R}_{105}$, - $(\text{CH}_2)_{0-4}-\text{NR}_{105}\text{R}'_{105}$, - $(\text{CH}_2)_{0-4}-\text{R}_{140}$, - $(\text{CH}_2)_{0-4}-\text{O-CO-}(\text{C}_1\text{-C}_6\text{ alkyl})$, - $(\text{CH}_2)_{0-4}-\text{O-P(O)-}(\text{O-R}_{110}\text{)}_2$, - $(\text{CH}_2)_{0-4}-\text{O-CO-N(R}_{150}\text{)}_2$, - $(\text{CH}_2)_{0-4}-\text{O-CS-N(R}_{150}\text{)}_2$, - $(\text{CH}_2)_{0-4}-\text{O-}(R_{150})$, - $(\text{CH}_2)_{0-4}-\text{O-R}_{150}'-\text{COOH}$, -
30

$(CH_2)_{0-4}-S-(R_{150})$, $-(CH_2)_{0-4}-N(R_{150})-SO_2-R_{105}$, $-(CH_2)_{0-4}-C_3-C_7$ cycloalkyl, (C_2-C_{10}) alkenyl, or (C_2-C_{10}) alkynyl.

Preferred compounds of formula I-2 include compounds wherein

5 R_N is $-C(=O)-R_{100}$; and

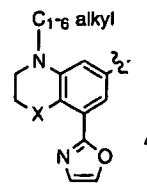
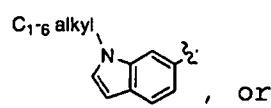
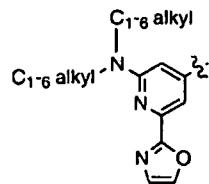
R_{100} represents aryl, or heteroaryl, where the ring portions of each are optionally substituted with 1, 2, or 3 groups independently selected from

10 $-OR$, $-NO_2$, C_1-C_6 alkyl, halogen, $-C\equiv N$, $-OCF_3$, $-CF_3$, $-(CH_2)_{0-4}-O-P(=O)(OR)(OR')$, $-(CH_2)_{0-4}-CO-NR_{105}R'_{105}$, $-(CH_2)_{0-4}-O-(CH_2)_{0-4}-CONR_{102}R_{102}'$, $-(CH_2)_{0-4}-CO-(C_1-C_{12})$ alkyl, $-(CH_2)_{0-4}-CO-(C_2-C_{12})$ alkenyl, $-(CH_2)_{0-4}-CO-(C_2-C_{12})$ alkynyl, $-(CH_2)_{0-4}-CO-(CH_2)_{0-4}(C_3-C_7)$ cycloalkyl, $-(CH_2)_{0-4}-R_{110}$, $-(CH_2)_{0-4}-R_{120}$, $-(CH_2)_{0-4}-R_{130}$, $-(CH_2)_{0-4}-CO-R_{110}$, $-(CH_2)_{0-4}-CO-R_{120}$, $-(CH_2)_{0-4}-CO-R_{130}$, $-(CH_2)_{0-4}-CO-R_{140}$, $-(CH_2)_{0-4}-CO-O-R_{150}$, $-(CH_2)_{0-4}-SO_2-NR_{105}R'_{105}$, $-(CH_2)_{0-4}-SO-(C_1-C_8)$ alkyl, $-(CH_2)_{0-4}-SO_2-(C_1-C_{12})$ alkyl, $-(CH_2)_{0-4}-SO_2-(CH_2)_{0-4}(C_3-C_7)$ cycloalkyl, $-(CH_2)_{0-4}-N(R_{150})-CO-O-R_{150}$, $-(CH_2)_{0-4}-N(R_{150})-CO-N(R_{150})_2$, $-(CH_2)_{0-4}-N(R_{150})-CS-N(R_{150})_2$, $-(CH_2)_{0-4}-N(R_{150})-CO-R_{105}$, $-(CH_2)_{0-4}-NR_{105}R'_{105}$, $-(CH_2)_{0-4}-R_{140}$, $-(CH_2)_{0-4}-O-CO-(C_1-C_6)$ alkyl, $-(CH_2)_{0-4}-O-P(O)-(O-R_{110})_2$, $-(CH_2)_{0-4}-O-CO-N(R_{150})_2$, $-(CH_2)_{0-4}-O-CS-N(R_{150})_2$, $-(CH_2)_{0-4}-O-(R_{150})$, $-(CH_2)_{0-4}-O-R_{150}'-COOH$, $-(CH_2)_{0-4}-S-(R_{150})$, $-(CH_2)_{0-4}-N(R_{150})-SO_2-R_{105}$, $-(CH_2)_{0-4}-C_3-C_7$ cycloalkyl, (C_2-C_{10}) alkenyl, or (C_2-C_{10}) alkynyl.

Preferred compounds of formula I-2 also include compounds wherein

R_N is $-C(=O)-R_{100}$; and

R_{100} is selected from phenyl, 1-naphthyl, 2-naphthyl, 30 tetralinyl, indanyl, dihydronaphthyl, 6,7,8,9-tetrahydro-5H-benzo[a]cycloheptenyl,



where X is CH, NH, O, or S, and where the ring portions of each are optionally substituted with 1, 2, or 3 groups independently selected from

5 -OR, -NO₂, C₁-C₆ alkyl, halogen, -C≡N, -OCF₃, -(CH₂)₀₋₄-O-P(=O)(OR)(OR'), -(CH₂)₀₋₄-CO-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-O-(CH₂)₀₋₄-CONR₁₀₂R₁₀₂', -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl), -(CH₂)₀₋₄-CO-(CH₂)₀₋₄(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-R₁₁₀,
10 -(CH₂)₀₋₄-R₁₂₀, -(CH₂)₀₋₄-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₁₀, -(CH₂)₀₋₄-CO-R₁₂₀, -(CH₂)₀₋₄-CO-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₄₀, -(CH₂)₀₋₄-CO-
15 O-R₁₅₀, -(CH₂)₀₋₄-SO₂-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-SO-(C₁-C₈ alkyl), -(CH₂)₀₋₄-SO₂-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-SO₂-(CH₂)₀₋₄-(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-N(R₁₅₀)-CO-O-R₁₅₀,
20 -(CH₂)₀₋₄-N(R₁₅₀)-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CS-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CO-R₁₀₅, -(CH₂)₀₋₄-NR₁₀₅R'₁₀₅,
-(CH₂)₀₋₄-R₁₄₀, -(CH₂)₀₋₄-O-CO-(C₁-C₆ alkyl), -(CH₂)₀₋₄-O-P(O)-(O-R₁₁₀)₂, -(CH₂)₀₋₄-O-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-O-CS-N(R₁₅₀)₂,
25 -(CH₂)₀₋₄-O-(R₁₅₀), -(CH₂)₀₋₄-O-R₁₅₀'-COOH, -(CH₂)₀₋₄-S-(R₁₅₀), -(CH₂)₀₋₄-N(R₁₅₀)-SO₂-R₁₀₅, -(CH₂)₀₋₄-C₃-C₇ cycloalkyl, (C₂-C₁₀) alkenyl, or (C₂-C₁₀) alkynyl.

Preferred compounds of formula I-2 also include compounds wherein

R_N is -C(=O)-phenyl optionally substituted with 1, 2, or 3 groups independently selected from

25 -OR, -NO₂, C₁-C₆ alkyl, halogen, -C≡N, -OCF₃, -CF₃, -(CH₂)₀₋₄-O-P(=O)(OR)(OR'), -(CH₂)₀₋₄-CO-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-O-(CH₂)₀₋₄-CONR₁₀₂R₁₀₂', -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl),
30 -(CH₂)₀₋₄-CO-(CH₂)₀₋₄(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-R₁₁₀, -(CH₂)₀₋₄-R₁₂₀, -(CH₂)₀₋₄-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₁₀, -(CH₂)₀₋₄-CO-R₁₂₀, -(CH₂)₀₋₄-CO-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₄₀, -(CH₂)₀₋₄-CO-
35 O-R₁₅₀, -(CH₂)₀₋₄-SO₂-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-SO-(C₁-C₈ alkyl), -(CH₂)₀₋₄-SO₂-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-SO₂-(CH₂)₀₋₄-(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-N(R₁₅₀)-CO-O-R₁₅₀,

$-\text{CH}_2\text{O-4-N(R}_{150}\text{)-CO-N(R}_{150}\text{)}_2$, $-\text{CH}_2\text{O-4-N(R}_{150}\text{)-CS-}$
 $\text{N(R}_{150}\text{)}_2$, $-\text{CH}_2\text{O-4-N(R}_{150}\text{)-CO-R}_{105}$, $-\text{CH}_2\text{O-4-NR}_{105}\text{R'}_{105}$,
 $-\text{CH}_2\text{O-4-R}_{140}$, $-\text{CH}_2\text{O-4-O-CO-(C}_1\text{-C}_6\text{ alkyl)}$, $-\text{CH}_2\text{O-4-O-}$
 $\text{P(O)-O-R}_{110}\text{)}_2$, $-\text{CH}_2\text{O-4-O-CO-N(R}_{150}\text{)}_2$, $-\text{CH}_2\text{O-4-O-CS-}$
5 $\text{N(R}_{150}\text{)}_2$, $-\text{CH}_2\text{O-4-O-(R}_{150}\text{)}$, $-\text{CH}_2\text{O-4-O-R}_{150}'\text{-COOH}$, $-\text{CH}_2\text{O-4-}$
 $\text{S-(R}_{150}\text{)}$, $-\text{CH}_2\text{O-4-N(R}_{150}\text{)-SO}_2\text{-R}_{105}$, $-\text{CH}_2\text{O-4-}$
 $\text{C}_3\text{-C}_7\text{ cycloalkyl}$, $(\text{C}_2\text{-C}_{10}\text{)alkenyl}$, or $(\text{C}_2\text{-C}_{10}\text{)alkynyl}$.

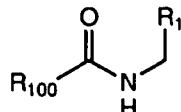
Preferred compounds of formula I-2 also include compounds wherein .

10 R_N is $-\text{C(=O)-phenyl}$ optionally substituted with 1 or 2 groups independently selected from $\text{C}_1\text{-C}_3$ alkyl, halogen, $-\text{SO}_2\text{-}$
 $\text{NR}_{105}\text{R'}_{105}$, $-\text{CO-NR}_{105}\text{R'}_{105}$, and $-\text{N(R}_{150}\text{)-SO}_2\text{-R}_{105}$, wherein
 R_{105} , R'_{105} and R_{150} are independently H or $\text{C}_1\text{-C}_6$ alkyl, or
15 R_{105} and R_{105}' together with the atom to which they are attached form a 3 to 7 membered carbocyclic ring.

Preferred compounds of formula I, I-1 and I-2 include compounds of formula I-3, i.e., those of formula I, I-1, or I-2 wherein

R_a represents hydrogen.

20 Preferred compounds of formula I-3 include compounds of formula I-3-a:



I-3-a

wherein

25 R_1 is $-\text{CH}_2\text{-phenyl}$ where the phenyl ring is optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, $\text{C}_1\text{-C}_4$ alkoxy, hydroxy, $-\text{NO}_2$, and

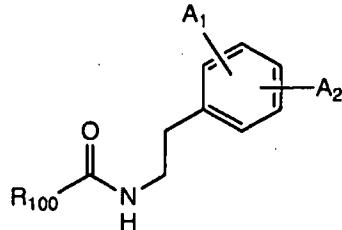
30 $\text{C}_1\text{-C}_4$ alkyl optionally substituted with 1, 2, or 3 substituents independently selected from halogen, OH, SH, NH₂, NH(C₁-C₆ alkyl), N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), C≡N, CF₃, or

C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 groups independently selected from $-SH$, $-C\equiv N$, C_1-C_3 alkoxy, $-S-(C_1-C_3)$ alkyl, amino, and mono- or dialkylamino; and

5 R_{100} represents aryl, or heteroaryl, where the ring portions of each are optionally substituted with 1, 2, or 3 groups independently selected from

$-OR$, $-NO_2$, C_1-C_6 alkyl, halogen, $-C\equiv N$, $-OCF_3$, $-CF_3$, $-(CH_2)_{0-4}-O-P(=O)(OR)(OR')$, $-(CH_2)_{0-4}-CO-NR_{105}R'_{105}$,
10 $-(CH_2)_{0-4}-O-(CH_2)_{0-4}-CONR_{102}R'_{102}$, $-(CH_2)_{0-4}-CO-(C_1-C_{12}$ alkyl), $-(CH_2)_{0-4}-CO-(C_2-C_{12}$ alkenyl), $-(CH_2)_{0-4}-CO-(C_2-C_{12}$ alkynyl), $-(CH_2)_{0-4}-CO-(CH_2)_{0-4}(C_3-C_7$ cycloalkyl), $-(CH_2)_{0-4}-R_{110}$, $-(CH_2)_{0-4}-R_{120}$, $-(CH_2)_{0-4}-R_{130}$, $-(CH_2)_{0-4}-CO-R_{110}$, $-(CH_2)_{0-4}-CO-R_{120}$, $-(CH_2)_{0-4}-CO-R_{130}$, $-(CH_2)_{0-4}-CO-R_{140}$, $-(CH_2)_{0-4}-CO-O-R_{150}$, $-(CH_2)_{0-4}-SO_2-NR_{105}R'_{105}$, $-(CH_2)_{0-4}-SO-(C_1-C_8$ alkyl), $-(CH_2)_{0-4}-SO_2-(C_1-C_{12}$ alkyl), $-(CH_2)_{0-4}-SO_2-(CH_2)_{0-4}-(C_3-C_7$ cycloalkyl), $-(CH_2)_{0-4}-N(R_{150})-CO-O-R_{150}$, $-(CH_2)_{0-4}-N(R_{150})-CO-N(R_{150})_2$, $-(CH_2)_{0-4}-N(R_{150})-CS-N(R_{150})_2$, $-(CH_2)_{0-4}-N(R_{150})-CO-R_{105}$, $-(CH_2)_{0-4}-NR_{105}R'_{105}$,
15 $-(CH_2)_{0-4}-R_{140}$, $-(CH_2)_{0-4}-O-CO-(C_1-C_6$ alkyl), $-(CH_2)_{0-4}-O-P(O)-(O-R_{110})_2$, $-(CH_2)_{0-4}-O-CO-N(R_{150})_2$, $-(CH_2)_{0-4}-O-CS-N(R_{150})_2$, $-(CH_2)_{0-4}-O-(R_{150})$, $-(CH_2)_{0-4}-O-R_{150}'-COOH$, $-(CH_2)_{0-4}-S-(R_{150})$, $-(CH_2)_{0-4}-N(R_{150})-SO_2-R_{105}$, $-(CH_2)_{0-4}-C_3-C_7$ cycloalkyl, (C_2-C_{10}) alkenyl, or (C_2-C_{10}) alkynyl.

20 25 Preferred compounds of the formula I-3-a include compounds of formula I-3-b:



I-3-b

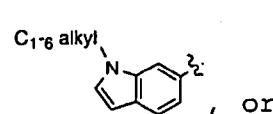
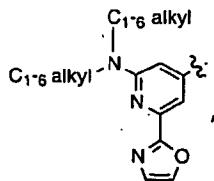
wherein

A_1 and A_2 are independently selected from halogen, C_1 - C_4 alkoxy, hydroxy, $-NO_2$, and C_1 - C_4 alkyl optionally substituted with 1, 2, or 3 substituents independently selected from halogen, OH, SH, NH_2 , $NH(C_1$ - C_6 alkyl), $N-(C_1$ - C_6 alkyl) $(C_1$ - C_6 alkyl), $C\equiv N$, CF_3 ; and

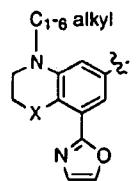
R_{100} represents aryl, or heteroaryl, where the ring portions of each are optionally substituted with 1, 2, or 3 groups independently selected from

-OR, $-NO_2$, C_1 - C_6 alkyl, halogen, $-C\equiv N$, $-OCF_3$, $-CF_3$, $-(CH_2)_{0-4}-O-P(=O)(OR)(OR')$, $-(CH_2)_{0-4}-CO-NR_{105}R'_{105}$, $-(CH_2)_{0-4}-O-(CH_2)_{0-4}-CONR_{102}R_{102}'$, $-(CH_2)_{0-4}-CO-(C_1-C_{12}$ alkyl), $-(CH_2)_{0-4}-CO-(C_2-C_{12}$ alkenyl), $-(CH_2)_{0-4}-CO-(C_2-C_{12}$ alkynyl), $-(CH_2)_{0-4}-CO-(CH_2)_{0-4}(C_3-C_7$ cycloalkyl), $-(CH_2)_{0-4}-R_{110}$, $-(CH_2)_{0-4}-R_{120}$, $-(CH_2)_{0-4}-R_{130}$, $-(CH_2)_{0-4}-CO-R_{110}$, $-(CH_2)_{0-4}-CO-R_{120}$, $-(CH_2)_{0-4}-CO-R_{130}$, $-(CH_2)_{0-4}-CO-R_{140}$, $-(CH_2)_{0-4}-CO-O-R_{150}$, $-(CH_2)_{0-4}-SO_2-NR_{105}R'_{105}$, $-(CH_2)_{0-4}-SO-(C_1-C_8$ alkyl), $-(CH_2)_{0-4}-SO_2-(C_1-C_{12}$ alkyl), $-(CH_2)_{0-4}-SO_2-(CH_2)_{0-4}-(C_3-C_7$ cycloalkyl), $-(CH_2)_{0-4}-N(R_{150})-CO-O-R_{150}$, $-(CH_2)_{0-4}-N(R_{150})-CO-N(R_{150})_2$, $-(CH_2)_{0-4}-N(R_{150})-CS-N(R_{150})_2$, $-(CH_2)_{0-4}-N(R_{150})-CO-R_{105}$, $-(CH_2)_{0-4}-NR_{105}R'_{105}$, $-(CH_2)_{0-4}-R_{140}$, $-(CH_2)_{0-4}-O-CO-(C_1-C_6$ alkyl), $-(CH_2)_{0-4}-O-P(O)-(O-R_{110})_2$, $-(CH_2)_{0-4}-O-CO-N(R_{150})_2$, $-(CH_2)_{0-4}-O-CS-N(R_{150})_2$, $-(CH_2)_{0-4}-O-(R_{150})$, $-(CH_2)_{0-4}-O-R_{150}'-COOH$, $-(CH_2)_{0-4}-S-(R_{150})$, $-(CH_2)_{0-4}-N(R_{150})-SO_2-R_{105}$, $-(CH_2)_{0-4}-C_3-C_7$ cycloalkyl, (C_2-C_{10}) alkenyl, or (C_2-C_{10}) alkynyl.

Preferred compounds of formula I-3-b include compounds wherein R_{100} is selected from phenyl, 1-naphthyl, 2-naphthyl, tetralinyl, indanyl, dihydronaphthyl, 6,7,8,9-tetrahydro-5H-benzo[a]cycloheptenyl,



, or



where X is CH, NH, O, or S, and where the ring portions of each are optionally substituted with 1, 2, or 3 groups independently selected from

5 -OR, -NO₂, C₁-C₆ alkyl, halogen, -C≡N, -OCF₃, -(CH₂)₀₋₄-O-P(=O)(OR)(OR'), -(CH₂)₀₋₄-CO-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-O-(CH₂)₀₋₄-CONR₁₀₂R₁₀₂', -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl), -(CH₂)₀₋₄-CO-(CH₂)₀₋₄(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-R₁₁₀, -(CH₂)₀₋₄-R₁₂₀, -(CH₂)₀₋₄-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₁₀, -(CH₂)₀₋₄-CO-R₁₂₀, -(CH₂)₀₋₄-CO-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₄₀, -(CH₂)₀₋₄-CO-O-R₁₅₀, -(CH₂)₀₋₄-SO₂-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-SO-(C₁-C₈ alkyl), -(CH₂)₀₋₄-SO₂-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-SO₂-(CH₂)₀₋₄(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-N(R₁₅₀)-CO-O-R₁₅₀, -(CH₂)₀₋₄-N(R₁₅₀)-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CS-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CO-R₁₀₅, -(CH₂)₀₋₄-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-R₁₄₀, -(CH₂)₀₋₄-O-CO-(C₁-C₆ alkyl), -(CH₂)₀₋₄-O-P(O)-(O-R₁₁₀)₂, -(CH₂)₀₋₄-O-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-O-CS-N(R₁₅₀)₂, -(CH₂)₀₋₄-O-(R₁₅₀), -(CH₂)₀₋₄-O-R₁₅₀-COOH, -(CH₂)₀₋₄-S-(R₁₅₀), -(CH₂)₀₋₄-N(R₁₅₀)-SO₂-R₁₀₅, -(CH₂)₀₋₄-C₃-C₇ cycloalkyl, (C₂-C₁₀) alkenyl, or (C₂-C₁₀) alkynyl.

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Preferred compounds of formula I-3-b also include compounds wherein

R₁₀₀ is phenyl where the phenyl is optionally substituted with 1, 2, or 3 groups independently selected from

25 -OR, -NO₂, halogen, -C≡N, -OCF₃, -CF₃, -(CH₂)₀₋₄-O-P(=O)(OR)(OR'), -(CH₂)₀₋₄-CO-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-O-(CH₂)₀₋₄-CONR₁₀₂R₁₀₂', -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl), -(CH₂)₀₋₄-CO-(CH₂)₀₋₄(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-R₁₁₀, -(CH₂)₀₋₄-R₁₂₀, -(CH₂)₀₋₄-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₁₀, -(CH₂)₀₋₄-CO-R₁₂₀, -(CH₂)₀₋₄-CO-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₄₀, -(CH₂)₀₋₄-CO-O-R₁₅₀, -(CH₂)₀₋₄-SO₂-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-SO-(C₁-C₈ alkyl), -(CH₂)₀₋₄-SO₂-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-SO₂-(CH₂)₀₋₄(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-N(R₁₅₀)-CO-O-R₁₅₀, -(CH₂)₀₋₄-N(R₁₅₀)-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CS-

30

35

$N(R_{150})_2$, $-(CH_2)_{0-4}-N(R_{150})-CO-R_{105}$, $-(CH_2)_{0-4}-NR_{105}R'_{105}$,
 $-(CH_2)_{0-4}-R_{140}$, $-(CH_2)_{0-4}-O-CO-(C_1-C_6\text{ alkyl})$, $-(CH_2)_{0-4}-O-$
 $P(O)-(O-R_{110})_2$, $-(CH_2)_{0-4}-O-CO-N(R_{150})_2$, $-(CH_2)_{0-4}-O-CS-$
 $N(R_{150})_2$, $-(CH_2)_{0-4}-O-(R_{150})$, $-(CH_2)_{0-4}-O-R_{150}'-COOH$, $-(CH_2)_{0-4}-S-(R_{150})$, $-(CH_2)_{0-4}-N(R_{150})-SO_2-R_{105}$, $-(CH_2)_{0-4}-C_3-C_7\text{ cycloalkyl}$, $(C_2-C_{10})\text{alkenyl}$, or $(C_2-C_{10})\text{alkynyl}$.
5

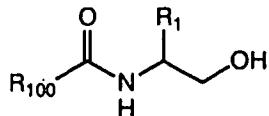
Preferred compounds of formula I-3-b also include compounds wherein

10 R_{100} is phenyl optionally substituted with 1 or 2 groups independently selected from halogen, $-SO_2-NR_{105}R'_{105}$, $-CO-NR_{105}R'_{105}$, and $-N(R_{150})-SO_2-R_{105}$, wherein R_{105} , R'_{105} and R_{150} are independently H or C_1-C_6 alkyl, or R_{105} and R_{105}' together with the atom to which they are attached form a 3 to 7 membered carbocyclic ring.
15

Preferred compounds of formula I, I-1 and I-2 include compounds of formula I-4, i.e., those of formula I, I-1, or I-2 wherein

R_a represents hydroxymethyl.

20 Preferred compounds of formula I-4 include compounds of formula I-4-a:



I-4-a

wherein

25 R_1 is $-CH_2\text{-phenyl}$ where the phenyl ring is optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, C_1-C_4 alkoxy, hydroxy, $-NO_2$, and

C_1-C_4 alkyl optionally substituted with 1, 2, or 3 substituents independently selected from halogen, OH, SH, NH_2 , $NH(C_1-C_6\text{ alkyl})$, $N-(C_1-C_6\text{ alkyl})(C_1-C_6\text{ alkyl})$,
30 $C\equiv N$, CF_3 , or

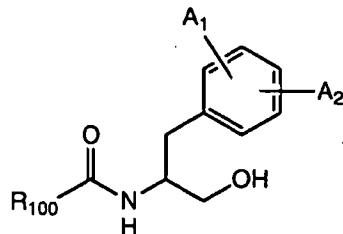
C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 groups independently selected from $-SH$, $-C\equiv N$, C_1-C_3 alkoxy,

-S-(C₁-C₃)alkyl, amino, and mono- or dialkylamino; and

R_{100} represents aryl, or heteroaryl, where the ring portions of each are optionally substituted with 1, 2, or 3 groups independently selected from

-OR, -NO₂, C₁-C₆ alkyl, halogen, -C≡N, -OCF₃, -CF₃, -
 (CH₂)₀₋₄-O-P(=O)(OR)(OR'), -(CH₂)₀₋₄-CO-NR₁₀₅R'₁₀₅,
 -(CH₂)₀₋₄-O-(CH₂)₀₋₄-CONR₁₀₂R'₁₀₂, -(CH₂)₀₋₄-CO-(C₁-C₁₂
 10 alkyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl), -(CH₂)₀₋₄-CO-(C₂-
 C₁₂ alkynyl), -(CH₂)₀₋₄-CO-(CH₂)₀₋₄(C₃-C₇ cycloalkyl),
 -(CH₂)₀₋₄-R₁₁₀, -(CH₂)₀₋₄-R₁₂₀, -(CH₂)₀₋₄-R₁₃₀, -(CH₂)₀₋₄-CO-
 R₁₁₀, -(CH₂)₀₋₄-CO-R₁₂₀, -(CH₂)₀₋₄-CO-R₁₃₀, -(CH₂)₀₋₄-CO-
 R₁₄₀, -(CH₂)₀₋₄-CO-O-R₁₅₀, -(CH₂)₀₋₄-SO₂-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-
 15 SO₂-(C₁-C₈ alkyl), -(CH₂)₀₋₄-SO₂-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-
 SO₂-(CH₂)₀₋₄-(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-N(R₁₅₀)-CO-O-
 R₁₅₀, -(CH₂)₀₋₄-N(R₁₅₀)-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CS-
 N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CO-R₁₀₅, -(CH₂)₀₋₄-NR₁₀₅R'₁₀₅,
 -(CH₂)₀₋₄-R₁₄₀, -(CH₂)₀₋₄-O-CO-(C₁-C₆ alkyl), -(CH₂)₀₋₄-O-
 P(O)-(O-R₁₁₀)₂, -(CH₂)₀₋₄-O-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-O-CS-
 20 N(R₁₅₀)₂, -(CH₂)₀₋₄-O-(R₁₅₀), -(CH₂)₀₋₄-O-R₁₅₀'-COOH, -
 (CH₂)₀₋₄-S-(R₁₅₀), -(CH₂)₀₋₄-N(R₁₅₀)-SO₂-R₁₀₅, -(CH₂)₀₋₄-
 C₃-C₇ cycloalkyl, (C₂-C₁₀) alkenyl, or (C₂-C₁₀) alkynyl.

Preferred compounds of the formula I-4-a include compounds of formula I-4-b:



I-4-b

wherein

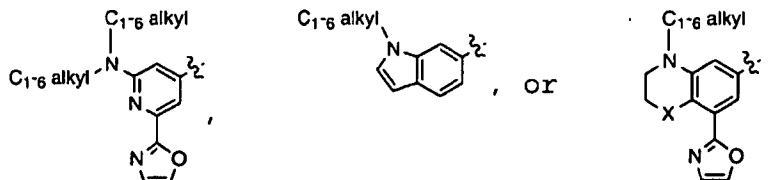
A_1 and A_2 are independently selected from halogen, C_1 - C_4 alkoxy, hydroxy, $-NO_2$, and C_1 - C_4 alkyl optionally substituted with 1, 2, or 3 substituents independently selected from

halogen, OH, SH, NH₂, NH(C₁-C₆ alkyl), N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), C≡N, CF₃; and

R₁₀₀ represents aryl, or heteroaryl, where the ring portions of each are optionally substituted with 1, 2, or 3 groups independently selected from

5 -OR, -NO₂, C₁-C₆ alkyl, halogen, -C≡N, -OCF₃, -CF₃, -(CH₂)₀₋₄-O-P(=O)(OR)(OR'), -(CH₂)₀₋₄-CO-NR₁₀₅R'₁₀₅,
-(CH₂)₀₋₄-O-(CH₂)₀₋₄-CONR₁₀₂R'₁₀₂, -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl), -(CH₂)₀₋₄-CO-(CH₂)₀₋₄(C₃-C₇ cycloalkyl),
10 -(CH₂)₀₋₄-R₁₁₀, -(CH₂)₀₋₄-R₁₂₀, -(CH₂)₀₋₄-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₁₀, -(CH₂)₀₋₄-CO-R₁₂₀, -(CH₂)₀₋₄-CO-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₄₀, -(CH₂)₀₋₄-CO-O-R₁₅₀, -(CH₂)₀₋₄-SO₂-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-SO-(C₁-C₈ alkyl), -(CH₂)₀₋₄-SO₂-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-SO₂-(CH₂)₀₋₄(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-N(R₁₅₀)-CO-O-R₁₅₀,
15 -(CH₂)₀₋₄-N(R₁₅₀)-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CS-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CO-R₁₀₅, -(CH₂)₀₋₄-NR₁₀₅R'₁₀₅,
-(CH₂)₀₋₄-R₁₄₀, -(CH₂)₀₋₄-O-CO-(C₁-C₆ alkyl), -(CH₂)₀₋₄-O-P(O)-(O-R₁₁₀)₂, -(CH₂)₀₋₄-O-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-O-CS-N(R₁₅₀)₂,
20 -(CH₂)₀₋₄-O-(R₁₅₀), -(CH₂)₀₋₄-O-R₁₅₀'-COOH, -(CH₂)₀₋₄-S-(R₁₅₀), -(CH₂)₀₋₄-N(R₁₅₀)-SO₂-R₁₀₅, -(CH₂)₀₋₄-C₃-C₇ cycloalkyl, (C₂-C₁₀) alkenyl, or (C₂-C₁₀) alkynyl.

Preferred compounds of formula I-4-b include compounds wherein R₁₀₀ is selected from phenyl, 1-naphthyl, 2-naphthyl, 25 tetralinyl, indanyl, dihydronaphthyl, 6,7,8,9-tetrahydro-5H-benzo[a]cycloheptenyl,



where X is CH, NH, O, or S, and where the ring portions of each are optionally substituted with 1, 2, or 3 groups independently selected from

30 -OR, -NO₂, C₁-C₆ alkyl, halogen, -C≡N, -OCF₃, -CF₃, -(CH₂)₀₋₄-O-P(=O)(OR)(OR'), -(CH₂)₀₋₄-CO-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-O-

$(CH_2)_{0-4}-CONR_{102}R_{102}'$, $-(CH_2)_{0-4}-CO-(C_1-C_{12} \text{ alkyl})$, $-(CH_2)_{0-4}-CO-(C_2-C_{12} \text{ alkenyl})$, $-(CH_2)_{0-4}-CO-(C_2-C_{12} \text{ alkynyl})$,
 $-(CH_2)_{0-4}-CO-(CH_2)_{0-4}(C_3-C_7 \text{ cycloalkyl})$, $-(CH_2)_{0-4}-R_{110}$,
 $-(CH_2)_{0-4}-R_{120}$, $-(CH_2)_{0-4}-R_{130}$, $-(CH_2)_{0-4}-CO-R_{110}$, $-(CH_2)_{0-4}-CO-R_{120}$,
 $-(CH_2)_{0-4}-CO-R_{130}$, $-(CH_2)_{0-4}-CO-R_{140}$, $-(CH_2)_{0-4}-CO-O-R_{150}$,
 $-(CH_2)_{0-4}-SO_2-NR_{105}R'_{105}$, $-(CH_2)_{0-4}-SO-(C_1-C_8 \text{ alkyl})$,
 $-(CH_2)_{0-4}-SO_2-(C_1-C_{12} \text{ alkyl})$, $-(CH_2)_{0-4}-SO_2-(CH_2)_{0-4}(C_3-C_7 \text{ cycloalkyl})$,
 $-(CH_2)_{0-4}-N(R_{150})-CO-O-R_{150}$, $-(CH_2)_{0-4}-N(R_{150})-CO-N(R_{150})_2$,
 $-(CH_2)_{0-4}-N(R_{150})-CO-R_{105}$, $-(CH_2)_{0-4}-NR_{105}R'_{105}$,
 $-(CH_2)_{0-4}-R_{140}$, $-(CH_2)_{0-4}-O-CO-(C_1-C_6 \text{ alkyl})$, $-(CH_2)_{0-4}-O-P(O)-(O-R_{110})_2$,
 $-(CH_2)_{0-4}-O-CO-N(R_{150})_2$, $-(CH_2)_{0-4}-O-CS-N(R_{150})_2$,
 $-(CH_2)_{0-4}-O-(R_{150})$, $-(CH_2)_{0-4}-O-R_{150}'-COOH$,
 $-(CH_2)_{0-4}-S-(R_{150})$, $-(CH_2)_{0-4}-N(R_{150})-SO_2-R_{105}$, $-(CH_2)_{0-4}-C_3-C_7 \text{ cycloalkyl}$, $(C_2-C_{10}) \text{ alkenyl}$, or $(C_2-C_{10}) \text{ alkynyl}$.

Preferred compounds of formula I-4-b also include compounds wherein

R_{100} is phenyl, 1-naphthyl or 2-naphthyl where the ring portions of each are optionally substituted with 1, 2, or 3 groups independently selected from

$-OR$, $-NO_2$, $C_1-C_6 \text{ alkyl}$, halogen, $-C\equiv N$, $-OCF_3$, $-CF_3$, $-(CH_2)_{0-4}-O-P(=O)(OR)(OR')$, $-(CH_2)_{0-4}-CO-NR_{105}R'_{105}$, $-(CH_2)_{0-4}-O-(CH_2)_{0-4}-CONR_{102}R_{102}'$, $-(CH_2)_{0-4}-CO-(C_1-C_{12} \text{ alkyl})$, $-(CH_2)_{0-4}-CO-(C_2-C_{12} \text{ alkenyl})$, $-(CH_2)_{0-4}-CO-(C_2-C_{12} \text{ alkynyl})$, $-(CH_2)_{0-4}-CO-(CH_2)_{0-4}(C_3-C_7 \text{ cycloalkyl})$, $-(CH_2)_{0-4}-R_{110}$,
 $-(CH_2)_{0-4}-R_{120}$, $-(CH_2)_{0-4}-R_{130}$, $-(CH_2)_{0-4}-CO-R_{110}$, $-(CH_2)_{0-4}-CO-R_{120}$, $-(CH_2)_{0-4}-CO-R_{130}$, $-(CH_2)_{0-4}-CO-R_{140}$, $-(CH_2)_{0-4}-CO-O-R_{150}$, $-(CH_2)_{0-4}-SO_2-NR_{105}R'_{105}$, $-(CH_2)_{0-4}-SO-(C_1-C_8 \text{ alkyl})$, $-(CH_2)_{0-4}-SO_2-(C_1-C_{12} \text{ alkyl})$, $-(CH_2)_{0-4}-SO_2-(CH_2)_{0-4}(C_3-C_7 \text{ cycloalkyl})$, $-(CH_2)_{0-4}-N(R_{150})-CO-O-R_{150}$,
 $-(CH_2)_{0-4}-N(R_{150})-CO-N(R_{150})_2$, $-(CH_2)_{0-4}-N(R_{150})-CS-N(R_{150})_2$, $-(CH_2)_{0-4}-N(R_{150})-CO-R_{105}$, $-(CH_2)_{0-4}-NR_{105}R'_{105}$, $-(CH_2)_{0-4}-R_{140}$, $-(CH_2)_{0-4}-O-CO-(C_1-C_6 \text{ alkyl})$, $-(CH_2)_{0-4}-O-P(O)-(O-R_{110})_2$, $-(CH_2)_{0-4}-O-CO-N(R_{150})_2$, $-(CH_2)_{0-4}-O-CS-N(R_{150})_2$, $-(CH_2)_{0-4}-O-(R_{150})$, $-(CH_2)_{0-4}-O-R_{150}'-COOH$,

$(CH_2)_{0-4}-S-(R_{150})$, $-(CH_2)_{0-4}-N(R_{150})-SO_2-R_{105}$, $-(CH_2)_{0-4}-C_3-C_7$ cycloalkyl, (C_2-C_{10}) alkenyl, or (C_2-C_{10}) alkynyl.

Preferred compounds of formula I-4-b also include compounds wherein

5 R_{100} is phenyl, 1-naphthyl or 2-naphthyl where the ring portions of each are optionally substituted with 1 or 2 groups independently selected from C_1-C_3 alkyl, halogen, $-SO_2-NR_{105}R'_{105}$, $-CO-NR_{105}R'_{105}$, and $-N(R_{150})-SO_2-R_{105}$, wherein R_{105} , R'_{105} and R_{150} are independently H or C_1-C_6 alkyl, or R_{105} and R_{105}' together with the atom to which they are attached form a 3 to 7 membered carbocyclic ring.

10 Preferred compounds of formula I, I-1 and I-2 include compounds of formula I-5, i.e., those of formula I, I-1, or I-2
15 wherein

R_a represents $-CH(OH)CH_2CH_2R_{120}$, or $-CH(OH)CH_2CH_2R_{130}$.

Preferred compounds of formula I-5 also include compounds wherein

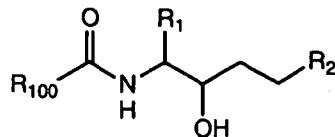
20 R_a represents $-CH(OH)CH_2CH_2$ -pyrrolyl, $-CH(OH)CH_2CH_2$ -pyrazolyl, $-CH(OH)CH_2CH_2-[1,2,4]$ triazolyl, $-CH(OH)CH_2CH_2-[1,2,3]$ triazolyl, $-CH(OH)CH_2CH_2$ -indolyl, $-CH(OH)CH_2CH_2$ -benzimidazolyl, $-CH(OH)CH_2CH_2$ -pyrrolidinonyl, or $-CH(OH)CH_2CH_2$ -piperidinonyl, wherein each ring is optionally substituted with 1 or 2 R_{125} groups; and

25 R_{125} at each occurrence is independently halogen, amino, mono- or dialkylamino, $-OH$, $-C\equiv N$, $-SO_2-NH_2$, $-SO_2-NH-C_1-C_6$ alkyl, $-SO_2-N(C_1-C_6$ alkyl) $_2$, $-SO_2-(C_1-C_4$ alkyl), $-CO-NH_2$, $-CO-NH-C_1-C_6$ alkyl, or $-CO-N(C_1-C_6$ alkyl) $_2$, or C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently selected from C_1-C_3 alkyl, halogen, $-OH$, $-SH$, $-C\equiv N$, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- and dialkylamino, or

30 C_1-C_6 alkoxy optionally substituted with one, two or three of halogen.

35

Preferred compounds of formula I-5 include compounds of formula I-5-a:



I-5-a

wherein

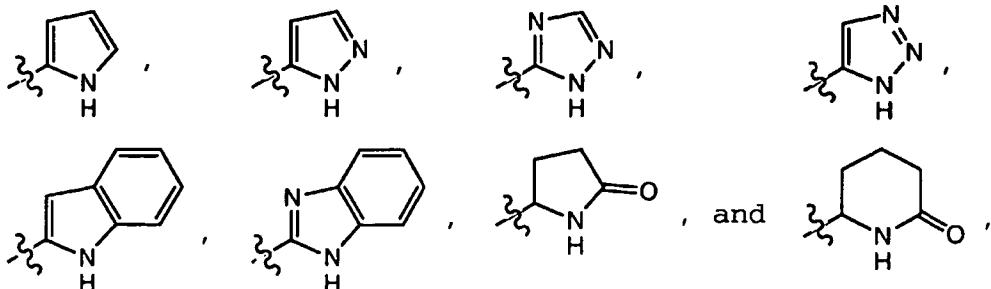
5 R₁ is -CH₂-phenyl where the phenyl ring is optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, C₁-C₄ alkoxy, hydroxy, -NO₂, and C₁-C₄ alkyl optionally substituted with 1, 2, or 3 substituents independently selected from halogen, OH, SH, NH₂, NH(C₁-C₆ alkyl), N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), C≡N, CF₃, or

10 C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from -SH, -C≡N, C₁-C₃ alkoxy, -S-(C₁-C₃)alkyl, amino, and mono- or dialkylamino;

15 R₁₀₀ represents aryl, or heteroaryl, where the ring portions of each are optionally substituted with 1, 2, or 3 groups independently selected from -OR, -NO₂, C₁-C₆ alkyl, halogen, -C≡N, -OCF₃, -CF₃, -(CH₂)₀₋₄-O-P(=O)(OR)(OR'), -(CH₂)₀₋₄-CO-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-O-(CH₂)₀₋₄-CONR₁₀₂R'₁₀₂, -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl), -(CH₂)₀₋₄-CO-(CH₂)₀₋₄(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-R₁₁₀, -(CH₂)₀₋₄-R₁₂₀, -(CH₂)₀₋₄-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₁₀, -(CH₂)₀₋₄-CO-R₁₂₀, -(CH₂)₀₋₄-CO-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₄₀, -(CH₂)₀₋₄-CO-O-R₁₅₀, -(CH₂)₀₋₄-SO₂-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-SO-(C₁-C₈ alkyl), -(CH₂)₀₋₄-SO₂-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-SO₂-(CH₂)₀₋₄(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-N(R₁₅₀)-CO-O-R₁₅₀, -(CH₂)₀₋₄-N(R₁₅₀)-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CS-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CO-R₁₀₅, -(CH₂)₀₋₄-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-R₁₄₀, -(CH₂)₀₋₄-O-CO-(C₁-C₆ alkyl), -(CH₂)₀₋₄-O-

$P(O)-(O-R_{110})_2$, $-(CH_2)_{0-4}-O-CO-N(R_{150})_2$, $-(CH_2)_{0-4}-O-CS-N(R_{150})_2$, $-(CH_2)_{0-4}-O-(R_{150})$, $-(CH_2)_{0-4}-O-R_{150}'-COOH$, $-(CH_2)_{0-4}-S-(R_{150})$, $-(CH_2)_{0-4}-N(R_{150})-SO_2-R_{105}$, $-(CH_2)_{0-4}-C_3-C_7$ cycloalkyl, (C_2-C_{10}) alkenyl, or (C_2-C_{10}) alkynyl;

5 R_2 is selected from



wherein each ring is optionally substituted with 1 or 2 R_{125} groups; and

R_{125} at each occurrence is independently halogen, amino, mono- or dialkylamino, $-OH$, $-C\equiv N$, $-SO_2-NH_2$, $-SO_2-NH-C_1-C_6$ alkyl,

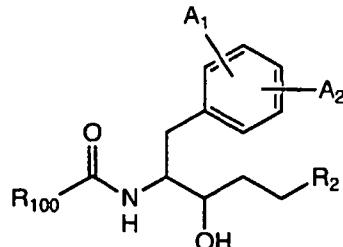
10 $-SO_2-N(C_1-C_6$ alkyl) $_2$, $-SO_2-(C_1-C_4$ alkyl), $-CO-NH_2$, $-CO-NH-C_1-C_6$ alkyl, or $-CO-N(C_1-C_6$ alkyl) $_2$, or

15 C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently selected from C_1-C_3 alkyl, halogen,

20 $-OH$, $-SH$, $-C\equiv N$, $-CF_3$, C_1-C_3 alkoxy, amino, and mono- and dialkylamino, or

C_1-C_6 alkoxy optionally substituted with one, two or three of halogen.

Preferred compounds of the formula I-5-a include compounds 20 of formula I-5-b:



I-5-b

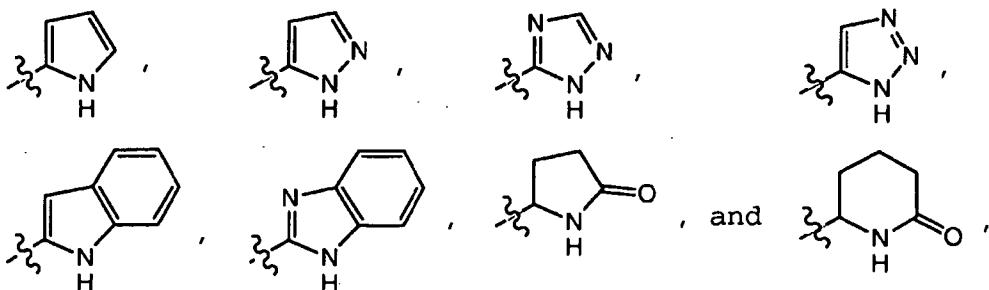
wherein

A₁ and A₂ are independently selected from halogen, C₁-C₄ alkoxy, hydroxy, -NO₂, and C₁-C₄ alkyl optionally substituted with 1, 2, or 3 substituents independently selected from halogen, OH, SH, NH₂, NH(C₁-C₆ alkyl), N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), C≡N, CF₃; and

R₁₀₀ represents aryl, or heteroaryl, where the ring portions of each are optionally substituted with 1, 2, or 3 groups independently selected from

-OR, -NO₂, C₁-C₆ alkyl, halogen, -C≡N, -OCF₃, -CF₃, -(CH₂)₀₋₄-O-P(=O)(OR)(OR'), -(CH₂)₀₋₄-CO-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-O-(CH₂)₀₋₄-CONR₁₀₂R'₁₀₂, -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl), -(CH₂)₀₋₄-CO-(CH₂)₀₋₄(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-R₁₁₀, -(CH₂)₀₋₄-R₁₂₀, -(CH₂)₀₋₄-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₁₀, -(CH₂)₀₋₄-CO-R₁₂₀, -(CH₂)₀₋₄-CO-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₄₀, -(CH₂)₀₋₄-CO-O-R₁₅₀, -(CH₂)₀₋₄-SO₂-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-SO-(C₁-C₈ alkyl), -(CH₂)₀₋₄-SO₂-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-SO₂-(CH₂)₀₋₄-(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-N(R₁₅₀)-CO-O-R₁₅₀, -(CH₂)₀₋₄-N(R₁₅₀)-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CS-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CO-R₁₀₅, -(CH₂)₀₋₄-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-R₁₄₀, -(CH₂)₀₋₄-O-CO-(C₁-C₆ alkyl), -(CH₂)₀₋₄-O-P(O)-(O-R₁₁₀)₂, -(CH₂)₀₋₄-O-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-O-CS-N(R₁₅₀)₂, -(CH₂)₀₋₄-O-(R₁₅₀), -(CH₂)₀₋₄-O-R₁₅₀'-COOH, -(CH₂)₀₋₄-S-(R₁₅₀), -(CH₂)₀₋₄-N(R₁₅₀)-SO₂-R₁₀₅, -(CH₂)₀₋₄-C₃-C₇ cycloalkyl, (C₂-C₁₀) alkenyl, or (C₂-C₁₀) alkynyl.

R₂ is selected from



wherein each ring is optionally substituted with 1 or 2 R₁₂₅ groups; and

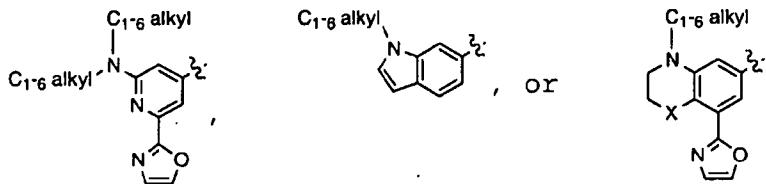
R_{125} at each occurrence is independently halogen, amino, mono- or dialkylamino, -OH, -C≡N, -SO₂-NH₂, -SO₂-NH-C₁-C₆ alkyl, -SO₂-N(C₁-C₆ alkyl)₂, -SO₂-(C₁-C₄ alkyl), -CO-NH₂, -CO-NH-C₁-C₆ alkyl, or -CO-N(C₁-C₆ alkyl)₂, or

5 C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently selected from C₁-C₃ alkyl, halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, and mono- and dialkylamino, or

10 C₁-C₆ alkoxy optionally substituted with one, two or three of halogen.

Preferred compounds of the formula I-5-b include compounds wherein A₁ and A₂ are both fluorine and are at the 3 and 5 positions of the phenyl ring.

15 Preferred compounds of formula I-5-b include compounds wherein R₁₀₀ is selected from phenyl, 1-naphthyl, 2-naphthyl, tetralinyl, indanyl, dihydronaphthyl, 6,7,8,9-tetrahydro-5H-benzo[a]cycloheptenyl,



20 where X is CH, NH, O, or S, and where the ring portions of each are optionally substituted with 1, 2, or 3 groups independently selected from

-OR, -NO₂, C₁-C₆ alkyl, halogen, -C≡N, -OCF₃, -CF₃, -(CH₂)₀₋₄-O-P(=O)(OR)(OR'), -(CH₂)₀₋₄-CO-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-O-(CH₂)₀₋₄-CONR₁₀₂R'₁₀₂, -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl), -(CH₂)₀₋₄-CO-(CH₂)₀₋₄(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-R₁₁₀, -(CH₂)₀₋₄-R₁₂₀, -(CH₂)₀₋₄-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₁₀, -(CH₂)₀₋₄-CO-R₁₂₀, -(CH₂)₀₋₄-CO-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₄₀, -(CH₂)₀₋₄-CO-O-R₁₅₀, -(CH₂)₀₋₄-SO₂-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-SO-(C₁-C₈ alkyl), -(CH₂)₀₋₄-SO₂-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-SO₂-

25

30

(CH₂)₀₋₄-(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-N(R₁₅₀)-CO-O-R₁₅₀,
 - (CH₂)₀₋₄-N(R₁₅₀)-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CS-
 N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CO-R₁₀₅, -(CH₂)₀₋₄-NR₁₀₅R'₁₀₅,
 - (CH₂)₀₋₄-R₁₄₀, -(CH₂)₀₋₄-O-CO-(C₁-C₆ alkyl), -(CH₂)₀₋₄-O-
 5 P(O)-(O-R₁₁₀)₂, -(CH₂)₀₋₄-O-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-O-CS-
 N(R₁₅₀)₂, -(CH₂)₀₋₄-O-(R₁₅₀), -(CH₂)₀₋₄-O-R₁₅₀'-COOH, -
 (CH₂)₀₋₄-S-(R₁₅₀), -(CH₂)₀₋₄-N(R₁₅₀)-SO₂-R₁₀₅, -(CH₂)₀₋₄-
 C₃-C₇ cycloalkyl, (C₂-C₁₀) alkenyl, or (C₂-C₁₀) alkynyl.

Preferred compounds of formula I-5-b also include
 10 compounds wherein

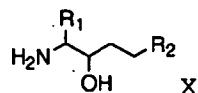
R₁₀₀ is phenyl optionally substituted with 1, 2, or 3 groups
 independently selected from
 -OR, -NO₂, C₁-C₆ alkyl, halogen, -C≡N, -OCF₃, -CF₃, -(CH₂)₀₋₄-
 15 -O-P(=O)(OR)(OR'), -(CH₂)₀₋₄-CO-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-O-(CH₂)₀₋₄-CONR₁₀₂R₁₀₂', -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-
 20 CO-(C₂-C₁₂ alkenyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl), -(CH₂)₀₋₄-CO-(CH₂)₀₋₄(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-R₁₁₀,
 -(CH₂)₀₋₄-R₁₂₀, -(CH₂)₀₋₄-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₁₀, -(CH₂)₀₋₄-
 25 CO-R₁₂₀, -(CH₂)₀₋₄-CO-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₄₀, -(CH₂)₀₋₄-CO-
 O-R₁₅₀, -(CH₂)₀₋₄-SO₂-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-SO-(C₁-C₈
 alkyl), -(CH₂)₀₋₄-SO₂-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-SO₂-(CH₂)₀₋₄-(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-N(R₁₅₀)-CO-O-R₁₅₀,
 -(CH₂)₀₋₄-N(R₁₅₀)-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CS-
 30 N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CO-R₁₀₅, -(CH₂)₀₋₄-NR₁₀₅R'₁₀₅,
 -(CH₂)₀₋₄-R₁₄₀, -(CH₂)₀₋₄-O-CO-(C₁-C₆ alkyl), -(CH₂)₀₋₄-O-
 P(O)-(O-R₁₁₀)₂, -(CH₂)₀₋₄-O-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-O-CS-
 N(R₁₅₀)₂, -(CH₂)₀₋₄-O-(R₁₅₀), -(CH₂)₀₋₄-O-R₁₅₀'-COOH, -
 (CH₂)₀₋₄-S-(R₁₅₀), -(CH₂)₀₋₄-N(R₁₅₀)-SO₂-R₁₀₅, -(CH₂)₀₋₄-
 C₃-C₇ cycloalkyl, (C₂-C₁₀) alkenyl, or (C₂-C₁₀) alkynyl.

Preferred compounds of formula I-5-b also include
 35 compounds wherein

R₁₀₀ is phenyl optionally substituted with 1 or 2 groups
 independently selected from C₁-C₃ alkyl, halogen, -
 SO₂-NR₁₀₅R'₁₀₅, -CO-NR₁₀₅R'₁₀₅, and -N(R₁₅₀)-SO₂-R₁₀₅,
 wherein R₁₀₅, R'₁₀₅ and R₁₅₀ are independently H or C₁-

C_6 alkyl, or R_{105} and R_{105}' together with the atom to which they are attached form a 3 to 7 membered carbocyclic ring.

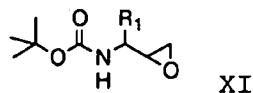
In another aspect, the invention provides intermediates of
5 the formula X:



wherein R_1 and R_2 are as defined for formula I.

The invention provides intermediates of the formula XI:

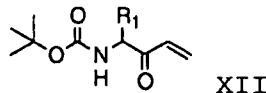
10



wherein R_1 is as defined for formula I.

The invention provides intermediates of the formula XII:

15.



wherein R_1 is as defined for formula I.

The invention provides intermediates of the formula XIII:

$$\begin{array}{c} \text{R}_1 \\ | \\ \text{H}_2\text{N} - \text{C} - \text{C} - \text{R}_a \\ | \\ \text{OH} \end{array} \quad \text{XIII}$$

20 wherein R_1 and R_a are as defined for formula I.

The invention also provides methods for treating a patient who has, or in preventing a patient from getting, a disease or condition selected from the group consisting of Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for treating patients with mild cognitive impairment (MCI) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-
30 Type; for treating cerebral amyloid angiopathy and preventing

its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia 5 associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, or diffuse Lewy body type of Alzheimer's disease and who is in need of such treatment which includes administration of a therapeutically effective amount of a compound of formula (I) or a 10 pharmaceutically acceptable salts thereof.

In an embodiment, this method of treatment can be used where the disease is Alzheimer's disease.

In an embodiment, this method of treatment can help prevent or delay the onset of Alzheimer's disease.

15 In an embodiment, this method of treatment can be used where the disease is mild cognitive impairment.

In an embodiment, this method of treatment can be used where the disease is Down's syndrome.

20 In an embodiment, this method of treatment can be used where the disease is Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type.

In an embodiment, this method of treatment can be used where the disease is cerebral amyloid angiopathy.

25 In an embodiment, this method of treatment can be used where the disease is degenerative dementias.

In an embodiment, this method of treatment can be used where the disease is diffuse Lewy body type of Alzheimer's disease.

30 In an embodiment, this method of treatment can treat an existing disease.

In an embodiment, this method of treatment can prevent a disease from developing.

35 In an embodiment, this method of treatment can employ therapeutically effective amounts: for oral administration from about 0.1 mg/day to about 1,000 mg/day; for parenteral,

sublingual, intranasal, intrathecal administration from about 0.5 to about 100 mg/day; for depo administration and implants from about 0.5 mg/day to about 50 mg/day; for topical administration from about 0.5 mg/day to about 200 mg/day; for 5 rectal administration from about 0.5 mg to about 500 mg.

In an embodiment, this method of treatment can employ therapeutically effective amounts: for oral administration from about 1 mg/day to about 100 mg/day; and for parenteral administration from about 5 to about 50 mg daily.

10 In an embodiment, this method of treatment can employ therapeutically effective amounts for oral administration from about 5 mg/day to about 50 mg/day.

15 The invention also includes pharmaceutical compositions which include a compound of formula (I) or a pharmaceutically acceptable salts thereof.

The invention also includes the use of a compound of formula (I) or pharmaceutically acceptable salts thereof for the manufacture of a medicament for use in treating a patient who has, or in preventing a patient from getting, a disease or 20 condition selected from the group consisting of Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for treating patients with mild cognitive impairment (MCI) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for 25 treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative dementias, 30 including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease and who is in need of such 35 treatment.

In an embodiment, this use of a compound of formula (I) can be employed where the disease is Alzheimer's disease.

In an embodiment, this use of a compound of formula (I) can help prevent or delay the onset of Alzheimer's disease.

5 In an embodiment, this use of a compound of formula (I) can be employed where the disease is mild cognitive impairment.

In an embodiment, this use of a compound of formula (I) can be employed where the disease is Down's syndrome.

10 In an embodiment, this use of a compound of formula (I) can be employed where the disease is Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type.

In an embodiment, this use of a compound of formula (I) can be employed where the disease is cerebral amyloid angiopathy.

15 In an embodiment, this use of a compound of formula (I) can be employed where the disease is degenerative dementias.

In an embodiment, this use of a compound of formula (I) can be employed where the disease is diffuse Lewy body type of Alzheimer's disease.

20 In an embodiment, this use of a compound employs a pharmaceutically acceptable salt selected from the group consisting of salts of the following acids hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, citric, methanesulfonic, $\text{CH}_3\text{-(CH}_2\text{)}_n\text{-COOH}$ where n is 0 thru 4, $\text{HOOC-(CH}_2\text{)}_n\text{-COOH}$ where n is as defined above, HOOC-CH=CH-COOH , and phenyl-COOH.

The invention also includes methods for inhibiting beta-secretase activity, for inhibiting cleavage of amyloid precursor protein (APP), in a reaction mixture, at a site 30 between Met596 and Asp597, numbered for the APP-695 amino acid isotype, or at a corresponding site of an isotype or mutant thereof; for inhibiting production of amyloid beta peptide (A beta) in a cell; for inhibiting the production of beta-amyloid plaque in an animal; and for treating or preventing a disease 35 characterized by beta-amyloid deposits in the brain. These

methods each include administration of a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salts thereof.

5 The invention also includes a method for inhibiting beta-secretase activity, including exposing said beta-secretase to an effective inhibitory amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

10 In an embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of less than 50 micromolar.

In an embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of 10 micromolar or less.

15 In an embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of 1 micromolar or less.

In an embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of 10 nanomolar or less.

20 In an embodiment, this method includes exposing said beta-secretase to said compound *in vitro*.

In an embodiment, this method includes exposing said beta-secretase to said compound in a cell.

25 In an embodiment, this method includes exposing said beta-secretase to said compound in a cell in an animal.

In an embodiment, this method includes exposing said beta-secretase to said compound in a human.

30 The invention also includes a method for inhibiting cleavage of amyloid precursor protein (APP), in a reaction mixture, at a site between Met596 and Asp597, numbered for the APP-695 amino acid isotype; or at a corresponding site of an isotype or mutant thereof, including exposing said reaction mixture to an effective inhibitory amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

In an embodiment, this method employs a cleavage site: between Met652 and Asp653, numbered for the APP-751 isotype; between Met 671 and Asp 672, numbered for the APP-770 isotype; between Leu596 and Asp597 of the APP-695 Swedish Mutation; 5 between Leu652 and Asp653 of the APP-751 Swedish Mutation; or between Leu671 and Asp672 of the APP-770 Swedish Mutation.

In an embodiment, this method exposes said reaction mixture *in vitro*.

10 In an embodiment, this method exposes said reaction mixture in a cell.

In an embodiment, this method exposes said reaction mixture in an animal cell.

In an embodiment, this method exposes said reaction mixture in a human cell.

15 The invention also includes a method for inhibiting production of amyloid beta peptide (A beta) in a cell, including administering to said cell an effective inhibitory amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

20 In an embodiment, this method includes administering to an animal.

In an embodiment, this method includes administering to a human.

25 The invention also includes a method for inhibiting the production of beta-amyloid plaque in an animal, including administering to said animal an effective inhibitory amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

30 In an embodiment, this method includes administering to a human.

The invention also includes a method for treating or preventing a disease characterized by beta-amyloid deposits in the brain including administering to a patient an effective therapeutic amount of a compound of formula (I), or a 35 pharmaceutically acceptable salt thereof.

In an embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of less than 50 micromolar.

5 In an embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of 10 micromolar or less.

In an embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of 1 micromolar or less.

10 In an embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of 10 nanomolar or less.

15 In an embodiment, this method employs a compound at a therapeutic amount in the range of from about 0.1 to about 1000 mg/day.

In an embodiment, this method employs a compound at a therapeutic amount in the range of from about 15 to about 1500 mg/day.

20 In an embodiment, this method employs a compound at a therapeutic amount in the range of from about 1 to about 100 mg/day.

In an embodiment, this method employs a compound at a therapeutic amount in the range of from about 5 to about 50 mg/day.

25 In an embodiment, this method can be used where said disease is Alzheimer's disease.

30 In an embodiment, this method can be used where said disease is Mild Cognitive Impairment, Down's Syndrome, or Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch Type.

The invention also includes a composition including beta-secretase complexed with a compound of formula (I), or a pharmaceutically acceptable salt thereof.

35 The invention also includes a method for producing a beta-secretase complex including exposing beta-secretase to a

compound of formula (I), or a pharmaceutically acceptable salt thereof, in a reaction mixture under conditions suitable for the production of said complex.

In an embodiment, this method employs exposing *in vitro*.

5 In an embodiment, this method employs a reaction mixture that is a cell.

The invention also includes a component kit including component parts capable of being assembled, in which at least one component part includes a compound of formula I enclosed in 10 a container.

In an embodiment, this component kit includes lyophilized compound, and at least one further component part includes a diluent.

The invention also includes a container kit including a 15 plurality of containers, each container including one or more unit dose of a compound of formula (I):, or a pharmaceutically acceptable salt thereof.

In an embodiment, this container kit includes each 20 container adapted for oral delivery and includes a tablet, gel, or capsule.

In an embodiment, this container kit includes each container adapted for parenteral delivery and includes a depot product, syringe, ampoule, or vial.

In an embodiment, this container kit includes each 25 container adapted for topical delivery and includes a patch, medipad, ointment, or cream.

The invention also includes an agent kit including a compound of formula (I), or a pharmaceutically acceptable salt thereof; and one or more therapeutic agent selected from the 30 group consisting of an antioxidant, an anti-inflammatory, a gamma secretase inhibitor, a neurotrophic agent, an acetyl cholinesterase inhibitor, a statin, an A beta peptide, and an anti-A beta antibody.

The invention also includes a composition including a compound of formula (I), or a pharmaceutically acceptable salt thereof; and an inert diluent or edible carrier.

5 In an embodiment, this composition includes a carrier that is an oil.

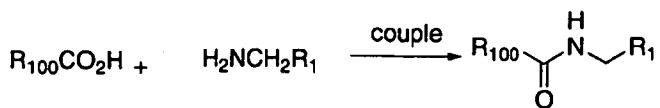
The invention also includes a composition including: a compound of formula (I), or a pharmaceutically acceptable salt thereof; and a binder, excipient, disintegrating agent, lubricant, or gildant.

10 The invention also includes a composition including a compound of formula (I), or a pharmaceutically acceptable salt thereof; disposed in a cream, ointment, or patch.

The invention provides compounds of formula (I) that are useful in treating and preventing Alzheimer's disease. The 15 compounds of the invention can be prepared by one skilled in the art based only on knowledge of the compound's chemical structure. The chemistry for the preparation of the compounds of this invention is known to those skilled in the art. In fact, there is more than one process to prepare the compounds of 20 the invention. Specific examples of methods of preparation can be found in the art. For examples, see *J. Med. Chem.* 1993, 36, 941-952; *J. Med. Chem.* 1991, 34, 2344-2356; *J. Med. Chem.* 1987, 30, 976-982; *Bioorg. Med. Chem. Lett.* 1999, 9, 3027-3030; *Bioorg. Med. Chem. Lett.* 1993, 3, 819-824; *J. Am. Chem. Soc.* 25 1996, 118, 8511-8517 and references cited therein. Such examples are also described in U.S. Patent No. 4,864,017, which is incorporated herein by reference, and references cited therein.

Examples of various processes that can be used to prepare 30 the compounds of the invention are set forth in the following Schemes. The groups R_1 , R_2 , R_N , R_a , and R_{100} carry the definitions set forth above for Formula I.

Scheme I

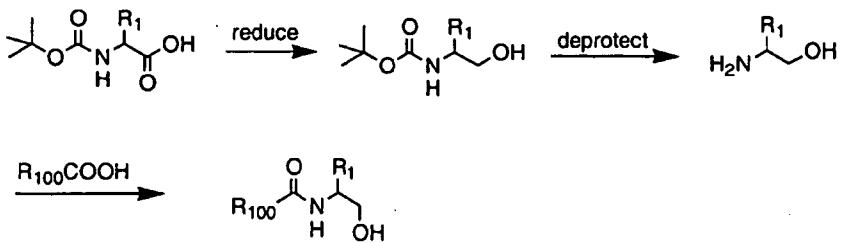


Accordingly, an acid is reacted with an amine $H_2NCH_2R_1$ in a mixture of, for example, DMF/DCM in the presence of a coupling agent such as 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride and a base such as dimethylaminopyridine.

5 Alternatively, an active ester may be prepared from the acid using, for example, Ethyl chloroformate, after which the active ester is reacted with the amine in a suitable solvent such as DMF or THF in the presence of base, e.g., triethylamine or dimethylaminopyridine.

10

Scheme II

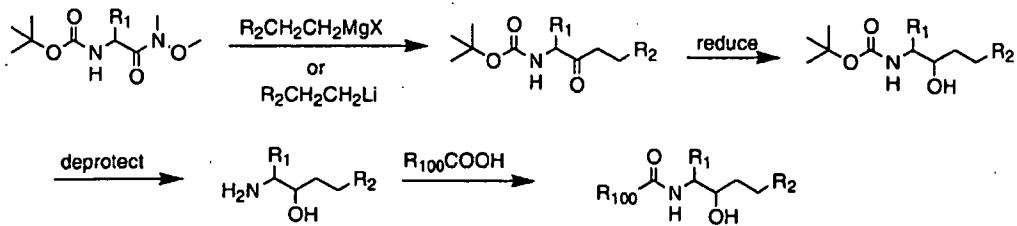


As shown in Scheme II, a protected amino acid is converted

15 to the corresponding alcohol using any of a variety of reducing agents, such as, for example, DIBAL or lithium aluminum hydride in an appropriate solvent. The alcohol can be deprotected using, for example, trifluoroacetic acid and the liberated amine can be coupled as described above with respect to Scheme

20 I.

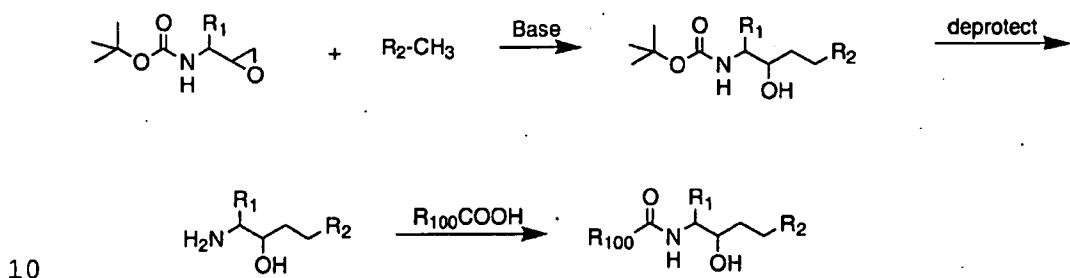
Scheme III



25 As shown in Scheme III, a protected N-methoxy-N-methyl amide is treated with an appropriate Grignard reagent $R_2CH_2CH_2MgX$ and the resulting ketone is reduced as described

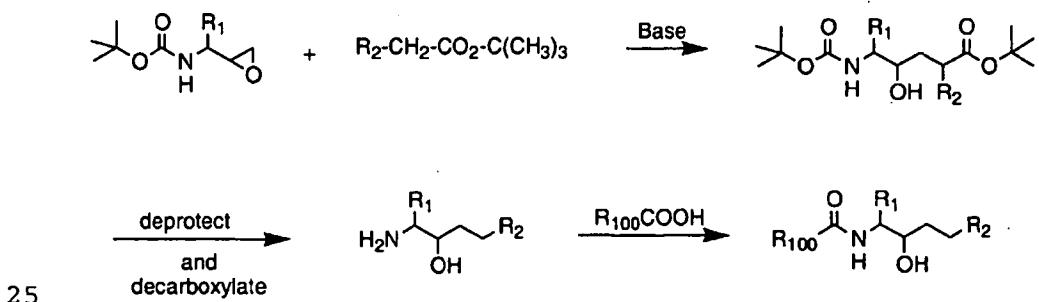
above and subsequently coupled with an acid as shown in Scheme I. In Scheme III, if R_2 contains an NH fragment, it may be necessary to use a suitable protecting group that would be removed at the end of the synthesis. Suitable protecting groups for NH are described, for example, in Green, T. W.; Wuts, Peter G.M. *Protective Groups in Organic Synthesis*, John Wiley and Sons, New York, (1999).

Scheme IV



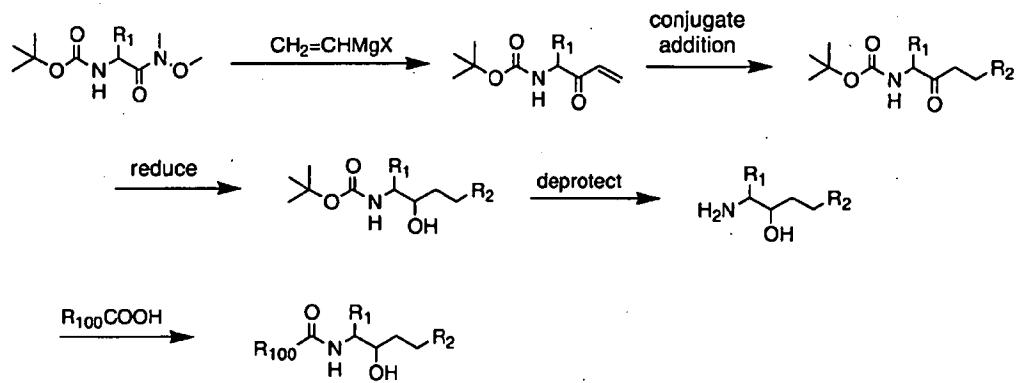
As shown in Scheme IV compound R_2CH_3 , in which R_2 is a suitably electron-withdrawing group, is deprotonated with a strong base such as lithium diisopropylamide and treated with a protected amino epoxide. Deprotection is performed followed by coupling to $\text{R}_{100}\text{COOH}$ using well-known methods. In Scheme IV, if R_2 contains an NH fragment, it may be necessary to use a suitable protecting group that is removed at the end of the synthesis. Suitable protecting groups for NH are described, for example, in Green, T. W.; Wuts, Peter G.M. *Protective Groups in Organic Synthesis*, John Wiley and Sons, New York, (1999).

Scheme V



A variation of the procedure in Scheme IV is shown in Scheme V. In this procedure a *tert*-butoxycarbonyl group is used as an acidity-enhancing group, thus permitting 5 deprotonation of the *pro*-nucleophile using less vigorous reaction conditions. The nucleophile-expoxide adduct is treated with a suitable acid to cleave the *tert*-butoxycarbonyl protecting group and to convert the *tert*-butoxy ester into a free carboxyl group. Decarboxylation at 25 °C or at elevated 10 temperatures is followed by coupling to $R_{100}COOH$ using well known methods. In Scheme V, if R_2 contains an NH fragment, it may be necessary to use a suitable protecting group that is removed at the end of the synthesis. Suitable protecting 15 groups for NH are described, for example, in Green, T. W.; Wuts, Peter G.M. *Protective Groups in Organic Synthesis*, John Wiley and Sons, New York, (1999).

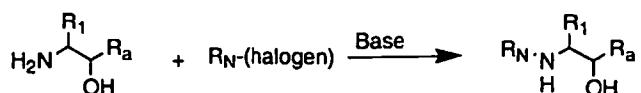
Scheme VI



20

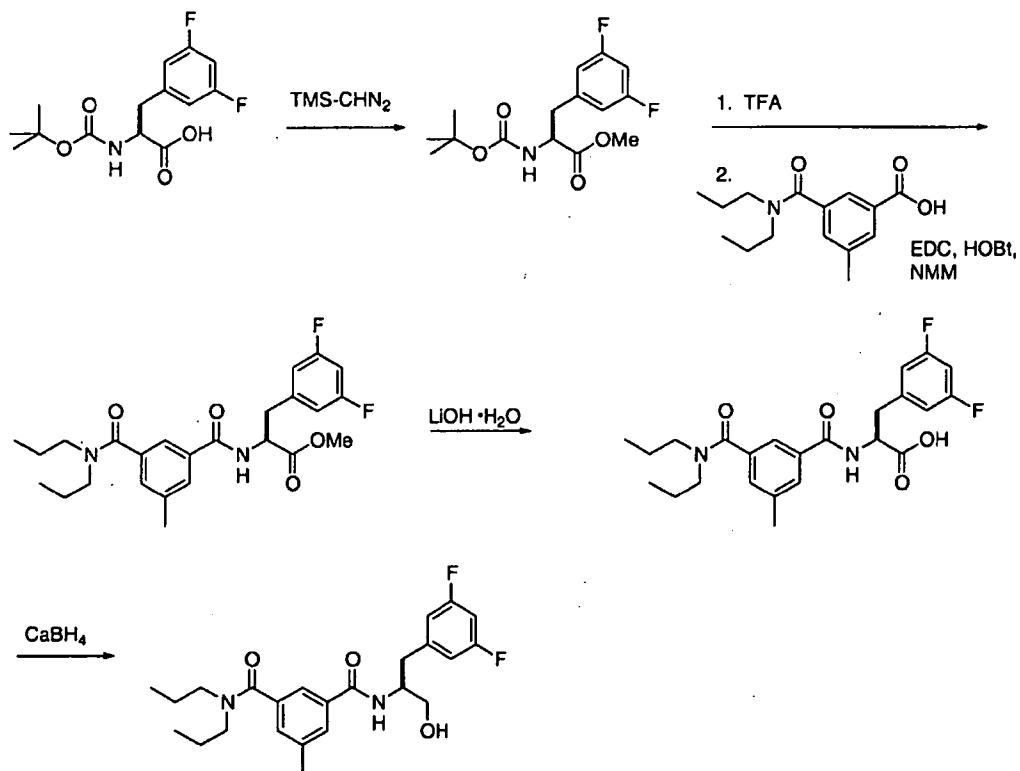
In Scheme VI, a Weinreb-amide is treated with a vinyl Gringard reagent to form a vinylic ketone. Conjugate addition of an organosodium, organolithium, organocuprate, organozinc, or a Gringard reagent to this ketone can be performed using 25 well-known procedures. The product is reduced, deprotected and coupled to $R_{100}COOH$ using well-known methods.

Scheme VII



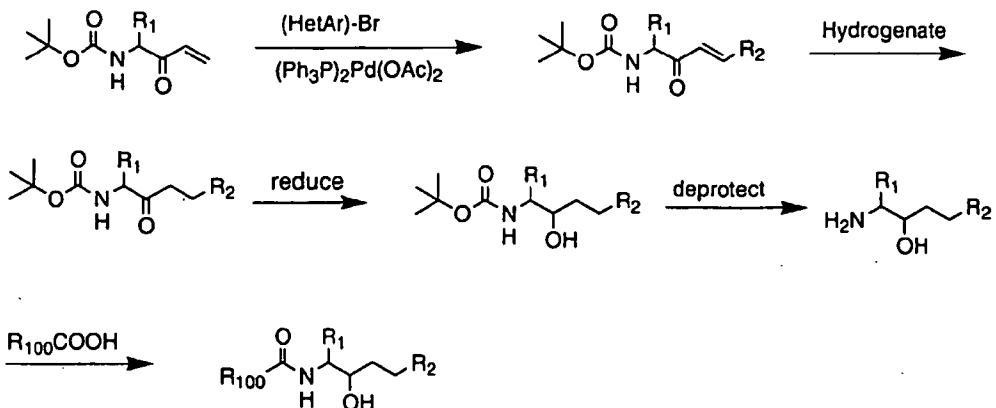
Compounds of general structure I, in which R_N is an acyl, 5 sulfonyl, aryl, heteroaryl, alkyl, heteroarylalkyl, arylalkyl, carbamoyl, or alkoxy carbonyl group can optionally be prepared as described in Scheme VII. The reaction rates and yields may be improved by the presence of a base, such as diisopropylethylamine or pyridine, and elevated temperatures 10 may be required in some cases.

Scheme VIII



15 In Scheme VIII, a protected amino acid is esterified and then deprotected. Acylation of the amino group with $\text{R}_{100}\text{COOH}$ is performed using well known methods. Hydrolysis of the carboxylic ester gives the acid which is then reduced.

Scheme IX



In Scheme IX, an enone prepared as in Scheme VI is treated
 5 with a heteroaryl bromide, a base such as triethylamine and a
 catalytic amount of a suitable palladium catalyst in hot
 dimethylformamide as solvent. The resulting adduct is
 hydrogenated, reduced, and the Boc protecting group removed by
 treatment with an acid such as TFA. Coupling to the acid R-
 10 $\text{R}_{100}\text{COOH}$ is then performed as described above.

The protection of amines is conducted, where appropriate, by methods known to those skilled in the art. Amino protecting groups are known to those skilled in the art. See for example, "Protecting Groups in Organic Synthesis", John Wiley and sons, 15 New York, N.Y., 1981, Chapter 7; "Protecting Groups in Organic Chemistry", Plenum Press, New York, N.Y., 1973, Chapter 2. When the amino protecting group is no longer needed, it is removed by methods known to those skilled in the art. By definition the amino protecting group must be readily 20 removable. A variety of suitable methodologies are known to those skilled in the art; see also T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry, John Wiley and Sons, 1991. Suitable amino protecting groups include t-butoxycarbonyl, benzyl-oxycarbonyl, formyl, trityl, 25 phthalimido, trichloro-acetyl, chloroacetyl, bromoacetyl, iodoacetyl, 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-ethoxybenzyloxycarbonyl, 4-

fluorobenzylloxycarbonyl, 4-chlorobenzylloxycarbonyl, 3-
 chlorobenzylloxycarbonyl, 2-chlorobenzylloxycarbonyl, 2,4-
 dichlorobenzylloxycarbonyl, 4-bromobenzylloxycarbonyl, 3-
 bromobenzylloxycarbonyl, 4-nitrobenzylloxycarbonyl, 4-
 5 cyanobenzylloxycarbonyl, 2-(4-xenyl)isopropoxycarbonyl, 1,1-
 diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-yloxycarbonyl,
 2-phenylprop-2-yloxycarbonyl, 2-(*p*-toluyl)prop-2-yloxy-
 carbonyl, cyclopentanyloxycarbonyl, 1-methylcyclo-
 pentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methyl-
 10 cyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-
 toluylsulfonyl)ethoxycarbonyl, 2-(methylsulfonyl)-
 ethoxycarbonyl, 2-(triphenylphosphino)ethoxycarbonyl,
 fluorenylmethoxycarbonyl, 2-(trimethylsilyl)ethoxy-carbonyl,
 allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-
 15 enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-
 acetoxybenzylloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-
 ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-
 (decyloxy)benzylloxycarbonyl, isobornyloxycarbonyl, 1-
 piperidyloxycarbonyl, 9-fluoroenylmethyl carbonate, -CH-CH=CH₂
 20 and phenyl-C(=N)-H.

It is preferred that the protecting group be *t*-butoxycarbonyl (BOC) and/or benzylloxycarbonyl (CBZ), it is more preferred that the protecting group be *t*-butoxycarbonyl. One skilled in the art will recognize suitable methods of introducing a *t*-butoxycarbonyl or benzylloxycarbonyl protecting group and may additionally consult T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry, John Wiley and Sons, 1991 for guidance.

The compounds of the invention may contain geometric or
 30 optical isomers as well as tautomers. Thus, the invention includes all tautomers and pure geometric isomers, such as the *E* and *Z* geometric isomers, as well as mixtures thereof. Further, the invention includes pure enantiomers and diastereomers as well as mixtures thereof, including racemic
 35 mixtures. The individual geometric isomers, enantiomers or

diastereomers may be prepared or isolated by methods known to those skilled in the art, including but not limited to chiral chromatography; preparing diastereomers, separating the diastereomers and converting the diastereomers into enantiomers 5 through the use of a chiral resolving agent.

Compounds of the invention with designated stereochemistry can be included in mixtures, including racemic mixtures, with other enantiomers, diastereomers, geometric isomers or tautomers. In a preferred aspect, compounds of the invention 10 with (S, R, R), (S, S, S), or (S, R, S) stereochemistry are typically present in these mixtures in excess of 50 percent. Preferably, compounds of the invention with designated stereochemistry are present in these mixtures in excess of 80 percent. More preferably, compounds of the invention with 15 designated stereochemistry are present in these mixtures in excess of 90 percent. Even more preferably, compounds of the invention with designated stereochemistry are present in these mixtures in excess of 99 percent.

Several of the compounds of formula (I) are amines, and as 20 such form salts when reacted with acids. Pharmaceutically acceptable salts are preferred over the corresponding amines of formula (I) since they produce compounds which are more water soluble, stable and/or more crystalline. Pharmaceutically acceptable salts are any salt which retains the activity of the 25 parent compound and does not impart any deleterious or undesirable effect on the subject to whom it is administered and in the context in which it is administered. Pharmaceutically acceptable salts include salts of both inorganic and organic acids. The preferred pharmaceutically acceptable 30 salts include salts of the following acids acetic, aspartic, benzenesulfonic, benzoic, bicarbonic, bisulfuric, bitartaric, butyric, calcium edetate, camsylic, carbonic, chlorobenzoic, citric, edetic, edisyllic, estolic, esyl, esylic, formic, fumaric, gluceptic, gluconic, glutamic, glycolylarsanilic, 35 hexamic, hexylresorcinic, hydrabamic, hydrobromic,

hydrochloric, hydroiodic, hydroxynaphthoic, isethionic, lactic, lactobionic, maleic, malic, malonic, mandelic, methanesulfonic, methylnitric, methylsulfuric, mucic, muconic, napsylic, nitric, oxalic, p-nitromethanesulfonic, pamoic, pantothenic, 5 phosphoric, monohydrogen phosphoric, dihydrogen phosphoric, phthalic, polygalactouronic, propionic, salicylic, stearic, succinic, succinic, sulfamic, sulfanilic, sulfonic, sulfuric, tannic, tartaric, teoclic and toluenesulfonic. For other acceptable salts, see *Int. J. Pharm.*, 33, 201-217 (1986) and *J. Pharm. Sci.*, 66(1), 1, (1977).

10 The invention provides compounds, compositions, kits, and methods for inhibiting beta-secretase enzyme activity and A beta peptide production. Inhibition of beta-secretase enzyme activity halts or reduces the production of A beta from APP and 15 reduces or eliminates the formation of beta-amyloid deposits in the brain.

Methods of the Invention

20 The compounds of the invention, and pharmaceutically acceptable salts thereof, are useful for treating humans or animals suffering from a condition characterized by a pathological form of beta-amyloid peptide, such as beta-amyloid plaques, and for helping to prevent or delay the onset of such a condition. For example, the compounds are useful for treating Alzheimer's disease, for helping prevent or delay the 25 onset of Alzheimer's disease, for treating patients with MCI (mild cognitive impairment) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the 30 Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobal hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's 35 disease, dementia associated with progressive supranuclear

palsy, dementia associated with cortical basal degeneration, and diffuse Lewy body type Alzheimer's disease. The compounds and compositions of the invention are particularly useful for treating or preventing Alzheimer's disease. When treating or 5 preventing these diseases, the compounds of the invention can either be used individually or in combination, as is best for the patient.

As used herein, the term "treating" means that the compounds of the invention can be used in humans with at least 10 a tentative diagnosis of disease. The compounds of the invention will delay or slow the progression of the disease thereby giving the individual a more useful life span.

The term "preventing" means that the compounds of the invention are useful when administered to a patient who has not 15 been diagnosed as possibly having the disease at the time of administration, but who would normally be expected to develop the disease or be at increased risk for the disease. The compounds of the invention will slow the development of disease symptoms, delay the onset of the disease, or prevent the 20 individual from developing the disease at all. Preventing also includes administration of the compounds of the invention to those individuals thought to be predisposed to the disease due to age, familial history, genetic or chromosomal abnormalities, and/or due to the presence of one or more biological markers 25 for the disease, such as a known genetic mutation of APP or APP cleavage products in brain tissues or fluids.

In treating or preventing the above diseases, the compounds of the invention are administered in a therapeutically effective amount. The therapeutically 30 effective amount will vary depending on the particular compound used and the route of administration, as is known to those skilled in the art.

In treating a patient displaying any of the diagnosed above conditions a physician may administer a compound of the 35 invention immediately and continue administration indefinitely,

as needed. In treating patients who are not diagnosed as having Alzheimer's disease, but who are believed to be at substantial risk for Alzheimer's disease, the physician should preferably start treatment when the patient first experiences 5 early pre-Alzheimer's symptoms such as, memory or cognitive problems associated with aging. In addition, there are some patients who may be determined to be at risk for developing Alzheimer's through the detection of a genetic marker such as APOE4 or other biological indicators that are predictive for 10 Alzheimer's disease. In these situations, even though the patient does not have symptoms of the disease, administration of the compounds of the invention may be started before symptoms appear, and treatment may be continued indefinitely to prevent or delay the onset of the disease.

15

Dosage Forms and Amounts

The compounds of the invention can be administered orally, parenterally, (IV, IM, depo-IM, SQ, and depo SQ), sublingually, intranasally (inhalation), intrathecally, topically, or 20 rectally. Dosage forms known to those of skill in the art are suitable for delivery of the compounds of the invention.

Compositions are provided that contain therapeutically effective amounts of the compounds of the invention. The compounds are preferably formulated into suitable 25 pharmaceutical preparations such as tablets, capsules, or elixirs for oral administration or in sterile solutions or suspensions for parenteral administration. Typically the compounds described above are formulated into pharmaceutical compositions using techniques and procedures well known in the 30 art.

About 1 to 500 mg of a compound or mixture of compounds of the invention or a physiologically acceptable salt or ester is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a 35 unit dosage form as called for by accepted pharmaceutical

practice. The amount of active substance in those compositions or preparations is such that a suitable dosage in the range indicated is obtained. The compositions are preferably formulated in a unit dosage form, each dosage containing from 5 about 2 to about 100 mg, more preferably about 10 to about 30 mg of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce 10 the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

To prepare compositions, one or more compounds of the invention are mixed with a suitable pharmaceutically acceptable carrier. Upon mixing or addition of the compound(s), the 15 resulting mixture may be a solution, suspension, emulsion, or the like. Liposomal suspensions may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. The form of the resulting mixture depends upon a number of factors, 20 including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for lessening or ameliorating at least one symptom of the disease, disorder, or condition treated and may be empirically determined.

25 Pharmaceutical carriers or vehicles suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration. In addition, the active materials can also be mixed with other active materials 30 that do not impair the desired action, or with materials that supplement the desired action, or have another action. The compounds may be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with other active ingredients.

Where the compounds exhibit insufficient solubility, methods for solubilizing may be used. Such methods are known and include, but are not limited to, using cosolvents such as dimethylsulfoxide (DMSO), using surfactants such as Tween®, and 5 dissolution in aqueous sodium bicarbonate. Derivatives of the compounds, such as salts or prodrugs may also be used in formulating effective pharmaceutical compositions.

The concentration of the compound is effective for delivery of an amount upon administration that lessens or 10 ameliorates at least one symptom of the disorder for which the compound is administered. Typically, the compositions are formulated for single dosage administration.

The compounds of the invention may be prepared with carriers that protect them against rapid elimination from the 15 body, such as time-release formulations or coatings. Such carriers include controlled release formulations, such as, but not limited to, microencapsulated delivery systems. The active compound is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful 20 effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration may be determined empirically by testing the compounds in known *in vitro* and *in vivo* model systems for the treated disorder.

The compounds and compositions of the invention can be 25 enclosed in multiple or single dose containers. The enclosed compounds and compositions can be provided in kits, for example, including component parts that can be assembled for use. For example, a compound inhibitor in lyophilized form and a suitable diluent may be provided as separated components for 30 combination prior to use. A kit may include a compound inhibitor and a second therapeutic agent for co-administration. The inhibitor and second therapeutic agent may be provided as separate component parts. A kit may include a plurality of containers, each container holding one or more unit dose of the 35 compound of the invention. The containers are preferably

adapted for the desired mode of administration, including, but not limited to tablets, gel capsules, sustained-release capsules, and the like for oral administration; depot products, pre-filled syringes, ampoules, vials, and the like for 5 parenteral administration; and patches, medipads, creams, and the like for topical administration.

The concentration of active compound in the drug composition will depend on absorption, inactivation, and excretion rates of the active compound, the dosage schedule, 10 and amount administered as well as other factors known to those of skill in the art.

The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage 15 and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be 20 alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration 25 ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

If oral administration is desired, the compound should be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can 30 be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

Oral compositions will generally include an inert diluent 35 or an edible carrier and may be compressed into tablets or

enclosed in gelatin capsules. For the purpose of oral therapeutic administration, the active compound or compounds can be incorporated with excipients and used in the form of tablets, capsules, or troches. Pharmaceutically compatible 5 binding agents and adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches, and the like can contain any of the following ingredients or compounds of a similar nature: a binder such as, but not limited to, gum 10 tragacanth, acacia, corn starch, or gelatin; an excipient such as microcrystalline cellulose, starch, or lactose; a disintegrating agent such as, but not limited to, alginic acid and corn starch; a lubricant such as, but not limited to, magnesium stearate; a gildant, such as, but not limited to, 15 colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; and a flavoring agent such as peppermint, methyl salicylate, or fruit flavoring.

When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such 20 as a fatty oil. In addition, dosage unit forms can contain various other materials, which modify the physical form of the dosage unit, for example, coatings of sugar and other enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the 25 like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings, and flavors.

The active materials can also be mixed with other active materials that do not impair the desired action, or with 30 materials that supplement the desired action.

Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include any of the following components: a sterile diluent such as water for injection, saline solution, fixed oil, a naturally occurring 35 vegetable oil such as sesame oil, coconut oil, peanut oil,

cottonseed oil, and the like, or a synthetic fatty vehicle such as ethyl oleate, and the like, polyethylene glycol, glycerine, propylene glycol, or other synthetic solvent; antimicrobial agents such as benzyl alcohol and methyl parabens; antioxidants 5 such as ascorbic acid and sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates, and phosphates; and agents for the adjustment of tonicity such as sodium chloride and dextrose. Parenteral preparations can be enclosed in ampoules, disposable 10 syringes, or multiple dose vials made of glass, plastic, or other suitable material. Buffers, preservatives, antioxidants, and the like can be incorporated as required.

Where administered intravenously, suitable carriers include physiological saline, phosphate buffered saline (PBS), 15 and solutions containing thickening and solubilizing agents such as glucose, polyethylene glycol, polypropylene glycol, and mixtures thereof. Liposomal suspensions including tissue-targeted liposomes may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to 20 methods known for example, as described in U.S. Patent No. 4,522,811.

The active compounds may be prepared with carriers that protect the compound against rapid elimination from the body, such as time-release formulations or coatings. Such carriers 25 include controlled release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid, and the like. Methods for 30 preparation of such formulations are known to those skilled in the art.

The compounds of the invention can be administered orally, parenterally (IV, IM, depo-IM, SQ, and depo-SQ), sublingually, intranasally (inhalation), intrathecally, topically, or

rectally. Dosage forms known to those skilled in the art are suitable for delivery of the compounds of the invention.

Compounds of the invention may be administered enterally or parenterally. When administered orally, compounds of the 5 invention can be administered in usual dosage forms for oral administration as is well known to those skilled in the art. These dosage forms include the usual solid unit dosage forms of tablets and capsules as well as liquid dosage forms such as solutions, suspensions, and elixirs. When the solid dosage 10 forms are used, it is preferred that they be of the sustained release type so that the compounds of the invention need to be administered only once or twice daily.

The oral dosage forms are administered to the patient 1, 2, 3, or 4 times daily. It is preferred that the compounds of 15 the invention be administered either three or fewer times, more preferably once or twice daily. Hence, it is preferred that the compounds of the invention be administered in oral dosage form. It is preferred that whatever oral dosage form is used, that it be designed so as to protect the compounds of the 20 invention from the acidic environment of the stomach. Enteric coated tablets are well known to those skilled in the art. In addition, capsules filled with small spheres each coated to protect from the acidic stomach, are also well known to those skilled in the art.

25 When administered orally, an administered amount therapeutically effective to inhibit beta-secretase activity, to inhibit A beta production, to inhibit A beta deposition, or to treat or prevent AD is from about 0.1 mg/day to about 1,000 mg/day. It is preferred that the oral dosage is from about 1 30 mg/day to about 100 mg/day. It is more preferred that the oral dosage is from about 5 mg/day to about 50 mg/day. It is understood that while a patient may be started at one dose, that dose may be varied over time as the patient's condition changes. In certain embodiments and situations, it may be 35 necessary to administer up to about 10 mg/kg or 30 mg/kg of the

compound per day, resulting in dosages of about, for example, 1500 mg/day or even about 2500 mg/day, either in one dose or two doses per day.

Compounds of the invention may also be advantageously 5 delivered in a nano crystal dispersion formulation. Preparation of such formulations is described, for example, in U.S. Patent 5,145,684. Nano crystalline dispersions of HIV protease inhibitors and their method of use are described in U.S. Patent No. 6,045,829. The nano crystalline formulations 10 typically afford greater bioavailability of drug compounds.

The compounds of the invention can be administered parenterally, for example, by IV, IM, depo-IM, SC, or depo-SC. When administered parenterally, a therapeutically effective amount of about 0.5 to about 100 mg/day, preferably from about 15 5 to about 50 mg daily should be delivered. When a depot formulation is used for injection once a month or once every two weeks, the dose should be about 0.5 mg/day to about 50 mg/day, or a monthly dose of from about 15 mg to about 1,500 mg. In part because of the forgetfulness of the patients with 20 Alzheimer's disease, it is preferred that the parenteral dosage form be a depo formulation.

The compounds of the invention can be administered sublingually. When given sublingually, the compounds of the invention should be given one to four times daily in the 25 amounts described above for IM administration.

The compounds of the invention can be administered intranasally. When given by this route, the appropriate dosage forms are a nasal spray or dry powder, as is known to those skilled in the art. The dosage of the compounds of the 30 invention for intranasal administration is the amount described above for IM administration.

The compounds of the invention can be administered intrathecally. When given by this route the appropriate dosage form can be a parenteral dosage form as is known to those 35 skilled in the art. The dosage of the compounds of the

invention for intrathecal administration is the amount described above for IM administration.

The compounds of the invention can be administered topically. When given by this route, the appropriate dosage 5 form is a cream, ointment, or patch. Because of the amount of the compounds of the invention to be administered, the patch is preferred. When administered topically, the dosage is from about 0.5 mg/day to about 200 mg/day. Because the amount that can be delivered by a patch is limited, two or more patches may 10 be used. The number and size of the patch is not important, what is important is that a therapeutically effective amount of the compounds of the invention be delivered as is known to those skilled in the art. The compounds of the invention can be administered rectally by suppository as is known to those 15 skilled in the art. When administered by suppository, the therapeutically effective amount is from about 0.5 mg to about 500 mg.

The compounds of the invention can be administered by implants as is known to those skilled in the art. When 20 administering a compound of the invention by implant, the therapeutically effective amount is the amount described above for depot administration.

Given a particular compound of the invention and a desired dosage form, one skilled in the art would know how to prepare 25 and administer the appropriate dosage form.

The compounds of the invention are used in the same manner, by the same routes of administration, using the same pharmaceutical dosage forms, and at the same dosing schedule as described above, for preventing disease or treating patients 30 with MCI (mild cognitive impairment) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating or preventing Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid 35 angiopathy and preventing its potential consequences, i.e.

single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, and diffuse Lewy body type of Alzheimer's disease.

The compounds of the invention can be used in combination, with each other or with other therapeutic agents or approaches used to treat or prevent the conditions listed above. Such agents or approaches include: acetylcholine esterase inhibitors such as tacrine (tetrahydroaminoacridine, marketed as COGNEX®), donepezil hydrochloride, (marketed as Aricept® and rivastigmine (marketed as Exelon®); gamma-secretase inhibitors; anti-inflammatory agents such as cyclooxygenase II inhibitors; anti-oxidants such as Vitamin E and ginkolides; immunological approaches, such as, for example, immunization with A beta peptide or administration of anti-A beta peptide antibodies; statins; and direct or indirect neurotropic agents such as Cerebrolysin®, AIT-082 (Emilieu, 2000, *Arch. Neurol.* 57:454), and other neurotropic agents of the future.

In addition, the compounds of formula (I) can also be used with inhibitors of P-glycoprotein (P-gp). P-gp inhibitors and the use of such compounds are known to those skilled in the art. See for example, *Cancer Research*, 53, 4595-4602 (1993), *Clin. Cancer Res.*, 2, 7-12 (1996), *Cancer Research*, 56, 4171-4179 (1996), International Publications WO99/64001 and WO01/10387. The important thing is that the blood level of the P-gp inhibitor be such that it exerts its effect in inhibiting P-gp from decreasing brain blood levels of the compounds of formula (A). To that end the P-gp inhibitor and the compounds of formula (A) can be administered at the same time, by the same or different route of administration, or at different times. The important thing is not the time of administration but having an effective blood level of the P-gp inhibitor.

Suitable P-gp inhibitors include cyclosporin A, verapamil, tamoxifen, quinidine, Vitamin E-TGPS, ritonavir, megestrol acetate, progesterone, rapamycin, 10,11-methanodibenzosuberane, phenothiazines, acridine derivatives such as GF120918, FK506, 5 VX-710, LY335979, PSC-833, GF-102,918 and other steroids. It is to be understood that additional agents will be found that have the same function and therefore achieve the same outcome; such compounds are also considered to be useful.

10 The P-gp inhibitors can be administered orally, parenterally, (IV, IM, IM-depo, SQ, SQ-depo), topically, sublingually, rectally, intranasally, intrathecally and by implant.

15 The therapeutically effective amount of the P-gp inhibitors is from about 0.1 to about 300 mg/kg/day, preferably about 0.1 to about 150 mg/kg daily. It is understood that while a patient may be started on one dose, that dose may have to be varied over time as the patient's condition changes.

20 When administered orally, the P-gp inhibitors can be administered in usual dosage forms for oral administration as is known to those skilled in the art. These dosage forms include the usual solid unit dosage forms of tablets and capsules as well as liquid dosage forms such as solutions, suspensions and elixirs. When the solid dosage forms are used, it is preferred that they be of the sustained release type so 25 that the P-gp inhibitors need to be administered only once or twice daily. The oral dosage forms are administered to the patient one thru four times daily. It is preferred that the P-gp inhibitors be administered either three or fewer times a day, more preferably once or twice daily. Hence, it is 30 preferred that the P-gp inhibitors be administered in solid dosage form and further it is preferred that the solid dosage form be a sustained release form which permits once or twice daily dosing. It is preferred that what ever dosage form is used, that it be designed so as to protect the P-gp inhibitors 35 from the acidic environment of the stomach. Enteric coated

tablets are well known to those skilled in the art. In addition, capsules filled with small spheres each coated to protect from the acidic stomach, are also well known to those skilled in the art.

5 In addition, the P-gp inhibitors can be administered parenterally. When administered parenterally they can be administered IV, IM, depo-IM, SQ or depo-SQ.

10 The P-gp inhibitors can be given sublingually. When given sublingually, the P-gp inhibitors should be given one thru four times daily in the same amount as for IM administration.

15 The P-gp inhibitors can be given intranasally. When given by this route of administration, the appropriate dosage forms are a nasal spray or dry powder as is known to those skilled in the art. The dosage of the P-gp inhibitors for intranasal administration is the same as for IM administration.

The P-gp inhibitors can be given intrathecally. When given by this route of administration the appropriate dosage form can be a parenteral dosage form as is known to those skilled in the art.

20 The P-gp inhibitors can be given topically. When given by this route of administration, the appropriate dosage form is a cream, ointment or patch. Because of the amount of the P-gp inhibitors needed to be administered the patch is preferred. However, the amount that can be delivered by a patch is 25 limited. Therefore, two or more patches may be required. The number and size of the patch is not important, what is important is that a therapeutically effective amount of the P-gp inhibitors be delivered as is known to those skilled in the art.

30 The P-gp inhibitors can be administered rectally by suppository as is known to those skilled in the art.

The P-gp inhibitors can be administered by implants as is known to those skilled in the art.

35 There is nothing novel about the route of administration nor the dosage forms for administering the P-gp inhibitors.

Given a particular P-gp inhibitor, and a desired dosage form, one skilled in the art would know how to prepare the appropriate dosage form for the P-gp inhibitor.

It should be apparent to one skilled in the art that the 5 exact dosage and frequency of administration will depend on the particular compounds of the invention administered, the particular condition being treated, the severity of the condition being treated, the age, weight, general physical condition of the particular patient, and other medication the 10 individual may be taking as is well known to administering physicians who are skilled in this art.

Inhibition of APP Cleavage

The compounds of the invention inhibit cleavage of APP 15 between Met595 and Asp596 numbered for the APP695 isoform, or a mutant thereof, or at a corresponding site of a different isoform, such as APP751 or APP770, or a mutant thereof (sometimes referred to as the "beta secretase site"). While not wishing to be bound by a particular theory, inhibition of 20 beta-secretase activity is thought to inhibit production of beta amyloid peptide (A beta). Inhibitory activity is demonstrated in one of a variety of inhibition assays, whereby cleavage of an APP substrate in the presence of a beta-secretase enzyme is analyzed in the presence of the inhibitory 25 compound, under conditions normally sufficient to result in cleavage at the beta-secretase cleavage site. Reduction of APP cleavage at the beta-secretase cleavage site compared with an untreated or inactive control is correlated with inhibitory activity. Assay systems that can be used to demonstrate 30 efficacy of the compound inhibitors of the invention are known. Representative assay systems are described, for example, in U.S. Patents No. 5,942,400, 5,744,346, as well as in the Examples below.

The enzymatic activity of beta-secretase and the 35 production of A beta can be analyzed *in vitro* or *in vivo*, using

natural, mutated, and/or synthetic APP substrates, natural, mutated, and/or synthetic enzyme, and the test compound. The analysis may involve primary or secondary cells expressing native, mutant, and/or synthetic APP and enzyme, animal models 5 expressing native APP and enzyme, or may utilize transgenic animal models expressing the substrate and enzyme. Detection of enzymatic activity can be by analysis of one or more of the cleavage products, for example, by immunoassay, fluorometric or chromogenic assay, HPLC, or other means of detection. 10 Inhibitory compounds are determined as those having the ability to decrease the amount of beta-secretase cleavage product produced in comparison to a control, where beta-secretase mediated cleavage in the reaction system is observed and measured in the absence of inhibitory compounds.

15

Beta-Secretase

Various forms of beta-secretase enzyme are known, and are available and useful for assay of enzyme activity and inhibition of enzyme activity. These include native, 20 recombinant, and synthetic forms of the enzyme. Human beta-secretase is known as Beta Site APP Cleaving Enzyme (BACE), Asp2, and memapsin 2, and has been characterized, for example, in U.S. Patent No. 5,744,346 and published PCT patent applications WO98/22597, WO00/03819, WO01/23533, and 25 WO00/17369, as well as in literature publications (Hussain et al., 1999, *Mol. Cell. Neurosci.* 14:419-427; Vassar et al., 1999, *Science* 286:735-741; Yan et al., 1999, *Nature* 402:533-537; Sinha et al., 1999, *Nature* 40:537-540; and Lin et al., 2000, *PNAS USA* 97:1456-1460). Synthetic forms of the enzyme 30 have also been described (WO98/22597 and WO00/17369). Beta-secretase can be extracted and purified from human brain tissue and can be produced in cells, for example mammalian cells expressing recombinant enzyme.

Preferred compounds are effective to inhibit 50% of beta- 35 secretase enzymatic activity at a concentration of less than 50

micromolar, preferably at a concentration of 10 micromolar or less, more preferably 1 micromolar or less, and most preferably 10 nanomolar or less.

5 **APP Substrate**

Assays that demonstrate inhibition of beta-secretase-mediated cleavage of APP can utilize any of the known forms of APP, including the 695 amino acid "normal" isotype described by Kang et al., 1987, *Nature* 325:733-6, the 770 amino acid isotype described by Kitaguchi et. al., 1981, *Nature* 331:530-532, and variants such as the Swedish Mutation (KM670-1NL) (APP-SW), the London Mutation (V7176F), and others. See, for example, U.S. Patent No. 5,766,846 and also Hardy, 1992, *Nature Genet.* 1:233-234, for a review of known variant mutations. Additional useful substrates include the dibasic amino acid modification, APP-KK disclosed, for example, in WO 00/17369, fragments of APP, and synthetic peptides containing the beta-secretase cleavage site, wild type (WT) or mutated form, e.g., SW, as described, for example, in U.S. Patent No 5,942,400 and WO00/03819.

The APP substrate contains the beta-secretase cleavage site of APP (KM-DA or NL-DA) for example, a complete APP peptide or variant, an APP fragment, a recombinant or synthetic APP, or a fusion peptide. Preferably, the fusion peptide includes the beta-secretase cleavage site fused to a peptide having a moiety useful for enzymatic assay, for example, having isolation and/or detection properties. A useful moiety may be an antigenic epitope for antibody binding, a label or other detection moiety, a binding substrate, and the like.

30

Antibodies

Products characteristic of APP cleavage can be measured by immunoassay using various antibodies, as described, for example, in Pirttila et al., 1999, *Neuro. Lett.* 249:21-4, and in U.S. Patent No. 5,612,486. Useful antibodies to detect A

beta include, for example, the monoclonal antibody 6E10 (Senetek, St. Louis, MO) that specifically recognizes an epitope on amino acids 1-16 of the A beta peptide; antibodies 162 and 164 (New York State Institute for Basic Research, 5 Staten Island, NY) that are specific for human A beta 1-40 and 1-42, respectively; and antibodies that recognize the junction region of beta-amyloid peptide, the site between residues 16 and 17, as described in U.S. Patent No. 5,593,846. Antibodies raised against a synthetic peptide of residues 591 to 596 of 10 APP and SW192 antibody raised against 590-596 of the Swedish mutation are also useful in immunoassay of APP and its cleavage products, as described in U.S. Patent Nos. 5,604,102 and 5,721,130.

15 **Assay Systems**

Assays for determining APP cleavage at the beta-secretase cleavage site are well known in the art. Exemplary assays, are described, for example, in U.S. Patent Nos. 5,744,346 and 5,942,400, and described in the Examples below.

20

Cell Free Assays

Exemplary assays that can be used to demonstrate the inhibitory activity of the compounds of the invention are described, for example, in WO00/17369, WO 00/03819, and U.S. 25 Patents No. 5,942,400 and 5,744,346. Such assays can be performed in cell-free incubations or in cellular incubations using cells expressing a beta-secretase and an APP substrate having a beta-secretase cleavage site.

An APP substrate containing the beta-secretase cleavage 30 site of APP, for example, a complete APP or variant, an APP fragment, or a recombinant or synthetic APP substrate containing the amino acid sequence: KM-DA or NL-DA, is incubated in the presence of beta-secretase enzyme, a fragment thereof, or a synthetic or recombinant polypeptide variant 35 having beta-secretase activity and effective to cleave the

beta-secretase cleavage site of APP, under incubation conditions suitable for the cleavage activity of the enzyme. Suitable substrates optionally include derivatives that may be fusion proteins or peptides that contain the substrate peptide and a modification useful to facilitate the purification or detection of the peptide or its beta-secretase cleavage products. Useful modifications include the insertion of a known antigenic epitope for antibody binding; the linking of a label or detectable moiety, the linking of a binding substrate, and the like.

Suitable incubation conditions for a cell-free *in vitro* assay include, for example: approximately 200 nanomolar to 10 micromolar substrate, approximately 10 to 200 picomolar enzyme, and approximately 0.1 nanomolar to 10 micromolar inhibitor compound, in aqueous solution, at an approximate pH of 4 -7, at approximately 37 degrees C, for a time period of approximately 10 minutes to 3 hours. These incubation conditions are exemplary only, and can be varied as required for the particular assay components and/or desired measurement system. Optimization of the incubation conditions for the particular assay components should account for the specific beta-secretase enzyme used and its pH optimum, any additional enzymes and/or markers that might be used in the assay, and the like. Such optimization is routine and will not require undue experimentation.

One useful assay utilizes a fusion peptide having maltose binding protein (MBP) fused to the C-terminal 125 amino acids of APP-SW. The MBP portion is captured on an assay substrate by anti-MBP capture antibody. Incubation of the captured fusion protein in the presence of beta-secretase results in cleavage of the substrate at the beta-secretase cleavage site. Analysis of the cleavage activity can be, for example, by immunoassay of cleavage products. One such immunoassay detects a unique epitope exposed at the carboxy terminus of the cleaved

fusion protein, for example, using the antibody SW192. This assay is described, for example, in U.S. Patent No 5,942,400.

Cellular Assay

5 Numerous cell-based assays can be used to analyze beta-secretase activity and/or processing of APP to release A beta. Contact of an APP substrate with a beta-secretase enzyme within the cell and in the presence or absence of a compound inhibitor of the invention can be used to demonstrate beta-secretase inhibitory activity of the compound. Preferably, assay in the presence of a useful inhibitory compound provides at least about 30%, most preferably at least about 50% inhibition of the enzymatic activity, as compared with a non-inhibited control.

15 In one embodiment, cells that naturally express beta-secretase are used. Alternatively, cells are modified to express a recombinant beta-secretase or synthetic variant enzyme as discussed above. The APP substrate may be added to the culture medium and is preferably expressed in the cells. Cells that naturally express APP, variant or mutant forms of 20 APP, or cells transformed to express an isoform of APP, mutant or variant APP, recombinant or synthetic APP, APP fragment, or synthetic APP peptide or fusion protein containing the beta-secretase APP cleavage site can be used, provided that the expressed APP is permitted to contact the enzyme and enzymatic 25 cleavage activity can be analyzed.

Human cell lines that normally process A beta from APP provide a useful means to assay inhibitory activities of the compounds of the invention. Production and release of A beta and/or other cleavage products into the culture medium can be 30 measured, for example by immunoassay, such as Western blot or enzyme-linked immunoassay (EIA) such as by ELISA.

Cells expressing an APP substrate and an active beta-secretase can be incubated in the presence of a compound inhibitor to demonstrate inhibition of enzymatic activity as 35 compared with a control. Activity of beta-secretase can be

measured by analysis of one or more cleavage products of the APP substrate. For example, inhibition of beta-secretase activity against the substrate APP would be expected to decrease release of specific beta-secretase induced APP cleavage products such as A beta.

5 Although both neural and non-neural cells process and release A beta, levels of endogenous beta-secretase activity are low and often difficult to detect by EIA. The use of cell types known to have enhanced beta-secretase activity, enhanced 10 processing of APP to A beta, and/or enhanced production of A beta are therefore preferred. For example, transfection of cells with the Swedish Mutant form of APP (APP-SW); with APP-KK; or with APP-SW-KK provides cells having enhanced beta-secretase activity and producing amounts of A beta that can be 15 readily measured.

In such assays, for example, the cells expressing APP and beta-secretase are incubated in a culture medium under conditions suitable for beta-secretase enzymatic activity at its cleavage site on the APP substrate. On exposure of the 20 cells to the compound inhibitor, the amount of A beta released into the medium and/or the amount of CTF99 fragments of APP in the cell lysates is reduced as compared with the control. The cleavage products of APP can be analyzed, for example, by immune reactions with specific antibodies, as discussed above.

25 Preferred cells for analysis of beta-secretase activity include primary human neuronal cells, primary transgenic animal neuronal cells where the transgene is APP, and other cells such as those of a stable 293 cell line expressing APP, for example, APP-SW.

30

In vivo Assays: Animal Models

Various animal models can be used to analyze beta-secretase activity and /or processing of APP to release A beta, as described above. For example, transgenic animals expressing 35 APP substrate and beta-secretase enzyme can be used to

demonstrate inhibitory activity of the compounds of the invention. Certain transgenic animal models have been described, for example, in U.S. Patent Nos.: 5,877,399; 5,612,486; 5,387,742; 5,720,936; 5,850,003; 5,877,015,, and 5 5,811,633, and in Ganes et al., 1995, *Nature* 373:523. Preferred are animals that exhibit characteristics associated with the pathophysiology of AD. Administration of the compound inhibitors of the invention to the transgenic mice described herein provides an alternative method for demonstrating the 10 inhibitory activity of the compounds. Administration of the compounds in a pharmaceutically effective carrier and via an administrative route that reaches the target tissue in an appropriate therapeutic amount is also preferred.

Inhibition of beta-secretase mediated cleavage of APP at 15 the beta-secretase cleavage site and of A beta release can be analyzed in these animals by measure of cleavage fragments in the animal's body fluids such as cerebral fluid or tissues. Analysis of brain tissues for A beta deposits or plaques is preferred.

On contacting an APP substrate with a beta-secretase enzyme in the presence of an inhibitory compound of the invention and under conditions sufficient to permit enzymatic mediated cleavage of APP and/or release of A beta from the substrate, the compounds of the invention are effective to 25 reduce beta-secretase-mediated cleavage of APP at the beta-secretase cleavage site and/or effective to reduce released amounts of A beta. Where such contacting is the administration of the inhibitory compounds of the invention to an animal model, for example, as described above, the compounds are 30 effective to reduce A beta deposition in brain tissues of the animal, and to reduce the number and/or size of beta amyloid plaques. Where such administration is to a human subject, the compounds are effective to inhibit or slow the progression of disease characterized by enhanced amounts of A beta, to slow

the progression of AD in the, and/or to prevent onset or development of AD in a patient at risk for the disease.

Unless defined otherwise, all scientific and technical terms used herein have the same meaning as commonly understood by one of skill in the art to which this invention belongs. All 5 patents and publications referred to herein are hereby incorporated by reference for all purposes.

Definitions

10 The definitions and explanations below are for the terms as used throughout this entire document including both the specification and the claims.

It should be noted that, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the content clearly dictates 15 otherwise. Thus, for example, reference to a composition containing "a compound" includes a mixture of two or more compounds. It should also be noted that the term "or" is generally employed in its sense including "and/or" unless the content clearly dictates otherwise.

20 The symbol "-" in general represents a bond between two atoms in the chain. Thus $\text{CH}_3\text{-O-CH}_2\text{-CH}(\text{R}_i)\text{-CH}_3$ represents a 2-substituted-1-methoxypropane compound. In addition, the symbol "-" represents the point of attachment of the substituent to a compound. Thus for example aryl($\text{C}_1\text{-C}_6$)alkyl- indicates an 25 alkylaryl group, such as benzyl, attached to the compound at the alkyl moiety.

Where multiple substituents are indicated as being attached to a structure, it is to be understood that the substituents can be the same or different. Thus for example 30 "R_m optionally substituted with 1, 2 or 3 R_q groups" indicates that R_m is substituted with 1, 2, or 3 R_q groups where the R_q groups can be the same or different.

APP, amyloid precursor protein, is defined as any APP polypeptide, including APP variants, mutations, and isoforms, 35 for example, as disclosed in U.S. Patent No. 5,766,846.

A beta, amyloid beta peptide, is defined as any peptide resulting from beta-secretase mediated cleavage of APP, including peptides of 39, 40, 41, 42, and 43 amino acids, and extending from the beta-secretase cleavage site to amino acids 5 39, 40, 41, 42, or 43.

Beta-secretase (BACE1, Asp2, Memapsin 2) is an aspartyl protease that mediates cleavage of APP at the amino-terminal edge of A beta. Human beta-secretase is described, for example, in WO00/17369.

10 Pharmaceutically acceptable refers to those properties and/or substances that are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, 15 patient acceptance and bioavailability.

A therapeutically effective amount is defined as an amount effective to reduce or lessen at least one symptom of the disease being treated or to reduce or delay onset of one or more clinical markers or symptoms of the disease.

20 By "alkyl" and "C₁-C₆ alkyl" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, such as, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. It is understood 25 that in cases where an alkyl chain of a substituent (e.g. of an alkyl, alkoxy or alkenyl group) is shorter or longer than 6 carbons, it will be so indicated in the second "C" as, for example, "C₁-C₁₀" indicates a maximum of 10 carbons.

30 By "alkoxy" and "C₁-C₆ alkoxy" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, attached through at least one divalent oxygen atom, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, isopentoxy, neopentoxy, hexoxy, and 3-methylpentoxy.

By the term "halogen" in the present invention is meant fluorine, bromine, chlorine, and iodine.

"Alkenyl" and "C₂-C₆ alkenyl" means straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and from 5 one to three double bonds and includes, for example, ethenyl, propenyl, 1-but-3-enyl, 1-pent-3-enyl, 1-hex-5-enyl and the like.

"Alkynyl" and "C₂-C₆ alkynyl" means straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and one or 10 two triple bonds and includes ethynyl, propynyl, butynyl, pentyn-2-yl and the like.

As used herein, the term "cycloalkyl" refers to saturated carbocyclic radicals having three to twelve carbon atoms. The cycloalkyl can be monocyclic, or a polycyclic fused system. 15 Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The cycloalkyl groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. For example, such cycloalkyl groups may be optionally substituted 20 with C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, amino(C₁-C₆)alkyl, mono(C₁-C₆)alkylamino(C₁-C₆)alkyl or di(C₁-C₆)alkylamino(C₁-C₆)alkyl.

25 By "aryl" is meant an aromatic carbocyclic group having a single ring (e.g., phenyl), multiple rings (e.g., biphenyl), or multiple condensed rings in which at least one is aromatic, (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl), which is optionally mono-, di-, or trisubstituted. Preferred aryl 30 groups of the present invention are phenyl, 1-naphthyl, 2-naphthyl, indanyl, indenyl, dihydronaphthyl, tetralinyl or 6,7,8,9-tetrahydro-5H-benzo[a]cycloheptenyl. The aryl groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. For example, such aryl groups may be optionally substituted with,

for example, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, amino(C_1-C_6)alkyl, mono(C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl, -COOH, -C(=O)O(C_1-C_6 alkyl), -C(=O)NH₂, -C(=O)N(mono- or di- C_1-C_6 alkyl), -S(C_1-C_6 alkyl), -SO₂(C_1-C_6 alkyl), -O-C(=O)(C_1-C_6 alkyl), -NH-C(=O)-(C_{1-C₆} alkyl), -N(C_1-C_6 alkyl)-C(=O)-(C_{1-C₆} alkyl), -NH-SO₂-(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)-SO₂-(C_1-C_6 alkyl), -NH-C(=O)NH₂, -NH-C(=O)N(mono- or di- C_1-C_6 alkyl), -NH(C_1-C_6 alkyl)-C(=O)-NH₂ or -NH(C_1-C_6 alkyl)-C(=O)-N(mono- or di- C_1-C_6 alkyl).

By "heteroaryl" is meant one or more aromatic ring systems of 5-, 6-, or 7-membered rings which includes fused ring systems of 9-11 atoms containing at least one and up to four heteroatoms selected from nitrogen, oxygen, or sulfur. Preferred heteroaryl groups of the present invention include pyridinyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl, indolinyl, pyridazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl, quinoxaliny, phthalazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indolizinyl, indazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxazolopyridinyl, imidazopyridinyl, isothiazolyl, naphthyridinyl, cinnolinyl, carbazolyl, betacarbolinyl, isochromanyl, chromanyl, tetrahydroisoquinolinyl, isoindolinyl, isobenzotetrahydrofuranol, isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl, pyridopyridinyl, benzotetrahydrofuranol, benzotetrahydrothienyl, purinyl, benzodioxolyl, triazinyl, phenoxazinyl, phenothiazinyl, pteridinyl, benzothiazolyl, imidazopyridinyl, imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl, dihydrobenzisothiazinyl, benzopyranol, benzothiopyranol, coumarinyl, isocoumarinyl, chromonyl, chromanonyl, pyridinyl-N-oxide, tetrahydroquinolinyl, dihydroquinolinyl, dihydroquinolinonyl, dihydroisoquinolinonyl,

dihydrocoumarinyl, dihydroisocoumarinyl, isoindolinonyl, benzodioxanyl, benzoxazolinonyl, pyrrolyl N-oxide, pyrimidinyl N-oxide, pyridazinyl N-oxide, pyrazinyl N-oxide, quinolinyl N-oxide, indolyl N-oxide, indolinyl N-oxide, isoquinolyl N-oxide, quinazolinyl N-oxide, quinoxalinyl N-oxide, phthalazinyl N-oxide, imidazolyl N-oxide, isoxazolyl N-oxide, oxazolyl N-oxide, thiazolyl N-oxide, indolizinyl N-oxide, indazolyl N-oxide, benzothiazolyl N-oxide, benzimidazolyl N-oxide, pyrrolyl N-oxide, oxadiazolyl N-oxide, thiadiazolyl N-oxide, triazolyl N-oxide, tetrazolyl N-oxide, benzothiopyranyl S-oxide, benzothiopyranyl S,S-dioxide. The heteroaryl groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. For example, such heteroaryl groups may be optionally substituted with C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, amino(C₁-C₆)alkyl, mono(C₁-C₆)alkylamino(C₁-C₆)alkyl or di(C₁-C₆)alkylamino(C₁-C₆)alkyl, -COOH, -C(=O)O(C₁-C₆ alkyl), -C(=O)NH₂, -C(=O)N(mono- or di-C₁-C₆ alkyl), -S(C₁-C₆ alkyl), -SO₂(C₁-C₆ alkyl), -O-C(=O)(C₁-C₆ alkyl), -NH-C(=O)-(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)-C(=O)-(C₁-C₆ alkyl), -NH-SO₂-(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)-SO₂-(C₁-C₆ alkyl), -NH-C(=O)NH₂, -NH-C(=O)N(mono- or di-C₁-C₆ alkyl), -NH(C₁-C₆ alkyl)-C(=O)-NH₂ or -NH(C₁-C₆ alkyl)-C(=O)-N-(mono- or di-C₁-C₆ alkyl).

By "heterocycle", "heterocycloalkyl" or "heterocyclyl" is meant one or more carbocyclic ring systems of 3-, 4-, 5-, 6-, or 7-membered rings which includes fused ring systems of 9-11 atoms containing at least one and up to four heteroatoms selected from nitrogen, oxygen, or sulfur. Preferred heterocycles of the present invention include morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperazinyl, homopiperazinyl, pyrrolidinyl, pyrrolidinonyl, pyrrolinyl, tetrahydropyranyl, piperidinyl, piperidinonyl, tetrahydrofuranyl, tetrahydrothienyl,

homopiperidinyl, homomorpholinyl, homothiomorpholinyl,
homothiomorpholinyl S,S-dioxide, oxazolidinonyl,
dihydropyrazolyl, dihydropyrrolyl, dihydropyrazinyl,
dihydropyridinyl, dihydropyrimidinyl, dihydrafuryl,
5 dihydropyranlyl, azepanyl, diazepanyl, tetrahydrothienyl S-
oxide, tetrahydrothienyl S,S-dioxide and homothiomorpholinyl S-
oxide. The heterocycle groups herein maybe unsubstituted or,
as specified, substituted in one or more substitutable
10 positions with various groups. For example, such heterocycle
groups may be optionally substituted with C₁-C₆ alkyl, C₁-C₆
alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C₁-
C₆)alkylamino, di(C₁-C₆)alkylamino, C₂-C₆alkenyl, C₂-C₆alkynyl,
C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, amino(C₁-C₆)alkyl, mono(C₁-
C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl or =O.
15 All patents and publications referred to herein are hereby
incorporated by reference for all purposes.

Structures were named using Name Pro IUPAC Naming
Software, version 5.09, available from Advanced Chemical
Development, Inc., 90 Adelaide Street West, Toronto, Ontario,
20 M5H 3V9, Canada.

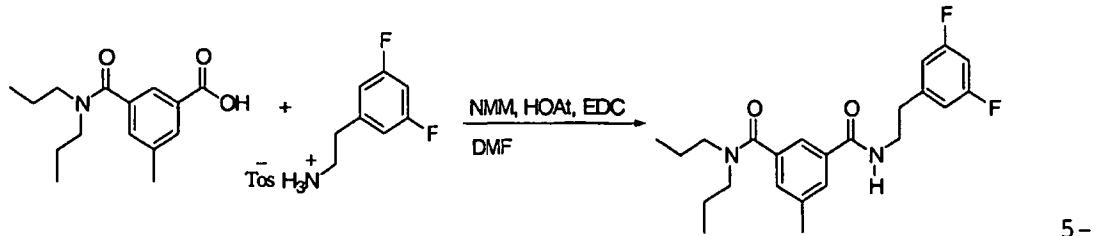
The present invention may be better understood with
reference to the following examples. These examples are
intended to be representative of specific embodiments of the
invention, and are not intended as limiting the scope of the
25 invention.

EXAMPLES

The following abbreviations may be used in the Examples:
EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or the
30 hydrochloride salt);
DIEA (diisopropylethylamine);
PyBOP (benzotriazol-1-yloxy)tritypyrrolidinophosphonium
hexafluorophosphate);
HATU (O-(7-azabenzotriazol-1-yl)-1,1,3,3-
35 tetramethyluronium hexafluorophosphate);

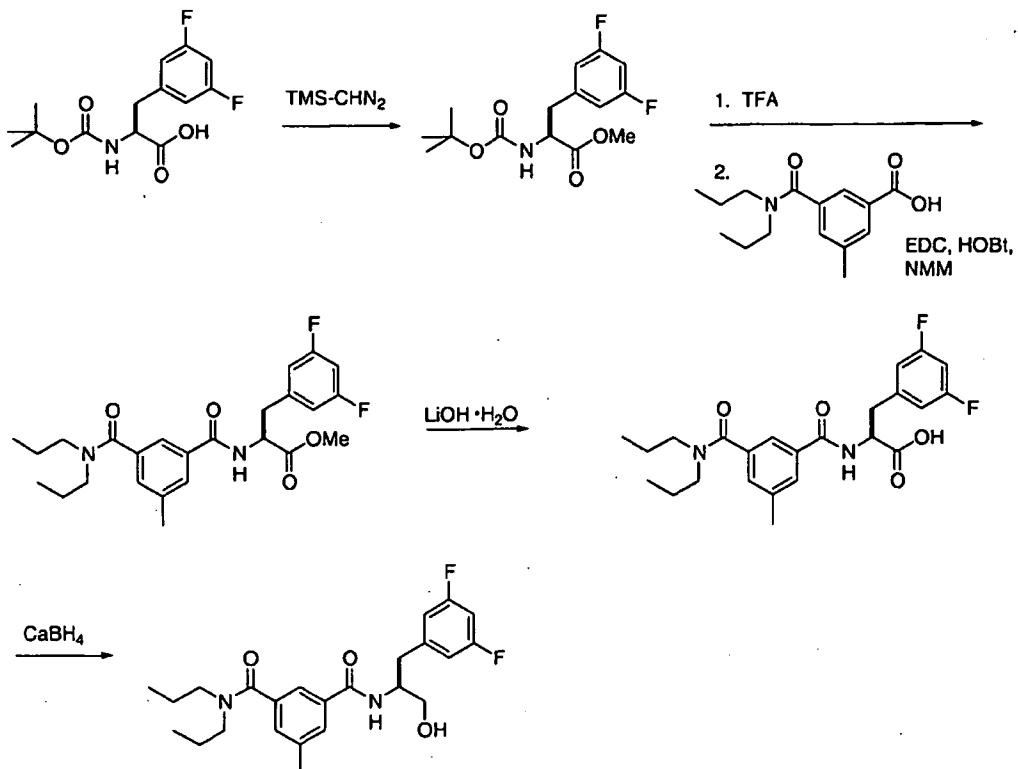
DCM (dichloromethane).

EXAMPLE 1: Synthesis of N-(3,5-Difluorophenyl-ethyl)-5-methyl-N',N'-dipropylisophthalamide from 5-methyl-N,N-dipropylisophthamic acid and 3,5-difluoro-phenethylamine.



Methyl-N, N-dipropylisophthamic acid (1.2 equiv, 0.25 mmol) was dissolved in dry DMF (10 mL) and the tosic acid salt of 3,5-difluorophenethylamine (1.0 equiv, 0.21 mmol) was added, followed by N-methyl morpholine (3.0 equiv, 0.21 mmol), 1-hydroxy-7-aza-benzotriazole (1.2 equiv, 0.25 mmol) and finally 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.3 equiv, 0.27 mmol). The resulting mixture was stirred at rt for 12 h. The reaction mixture was then diluted with 10% citric acid (aq), and extracted with ethyl acetate (3X). The combined organic extracts were washed (saturated NaHCO₃, saturated NaCl), dried (Na₂SO₄), filtered and concentrated under vacuum. This oil was purified by Prep Plate on SiO₂ with 70% EtOAc. M+H⁺ = 403.2.

EXAMPLE 2: Synthesis of N'-(1S)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-5-methyl-N,N-dipropyl-isophthalamide.

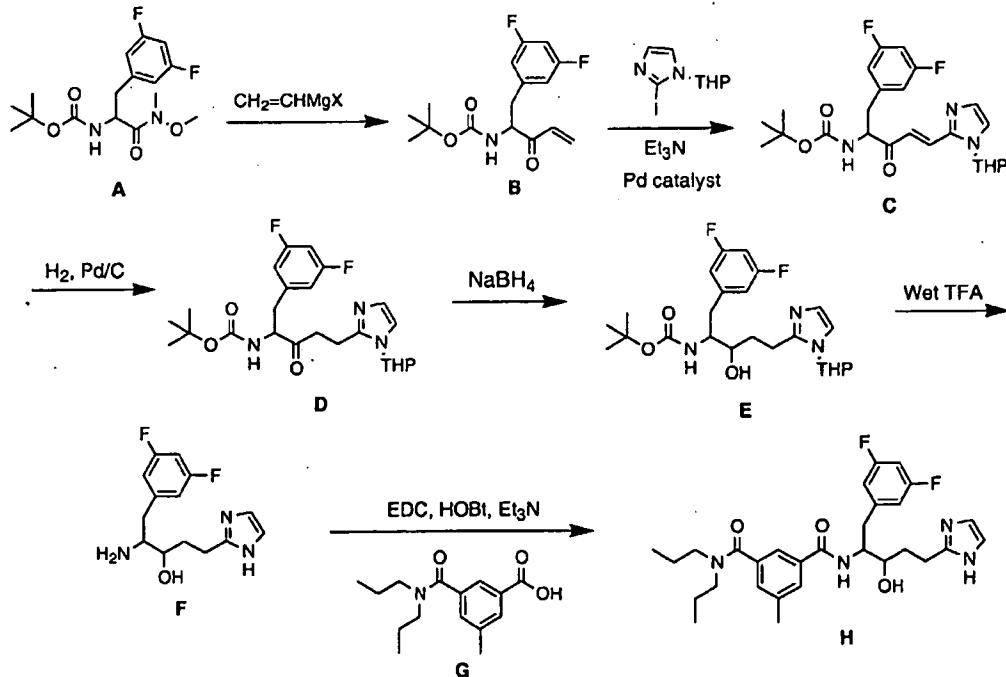


The boc-diflurorophenyl alanine (1 eq) was dissolved in 9:1 THF:MeOH and the reaction was cooled to 0 °C. TMS-CHN2 (3 eq) was slowly added to this mixture. After 2 h of stirring 5 while warming to RT the reaction was monitored by TLC. The reaction was complete after 4 h. The reaction mixture was cooled to 0°C and extracted between 1N HCl and ethylacetate. The organic layer was extracted with saturated bicarbonate, saturated brine and dried over sodium sulfate followed by 10 removal of solvent in vacuo. The product thus obtained was deprotected using 1:1 TFA/ CH2C12. The resulting amine (1 eq) was dissolved in THF and to this mixture added EDC, HOBT and N-methyl morphline. The coupling reaction was monitored by TLC and was found to be complete overnight. The reaction was 15 extracted between ethylacetate and brine. The organic layer was dried over MgSO4 and solvent removed in vacuo. The crude mixture was purified by flash chromatography to yield the pure coupled ester. The ester (0.5 eq) was dissolved in 1:1 THF:H2O and 5 equivalents of LiOH·H2O was added and the mixture 20 stirred overnight. The reaction appeared to be complete by

TLC. The reaction mixture was acidified with 1N HCl and extracted into ethylacetate. Removal of the solvent in vacuo yielded the desired carboxylic acid. $MH^+ = 449$.

The alcohol was formed as follows. $CaCl_2$ (1.5 eq) was dissolved in 2:1 THF ethanol and the reaction was cooled to $0^\circ C$. The carboxylic acid, 1 equivalent, was added followed by sodium borohydride (3 equivalents) in portions. Evolution of H_2 gas was observed. Consumption of acid was monitored by TLC. The reaction was complete in 4 hours. While maintaining the temperature at $0^\circ C$ the reaction was carefully acidified with excess acetic acid. Solvent was evaporated in vacuo, and the reaction was resuspended in ethylacetate, followed by washing with saturated sodium bicarbonate and saturated $NaCl$ solution. The solution was dried over magnesium sulfate, filtered and solvents evaporated. $MH^+ = 433.2$.

EXAMPLE 3: Synthesis of *N'*-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-imidazol-2-yl)butyl]-5-methyl-*N,N*-dipropylisophthalamide.



A 0 °C THF solution of the Weinreb amide **A** is treated with 2 molar equivalents of vinylmagnesium bromide. After stirring for an hour at 0 °C, the mixture is allowed to warm to room temperature and then it is poured onto ice. Saturated ammonium 5 chloride solution is added until all of the magnesium hydroxide precipitate dissolves and then the product is extracted into ethyl acetate. The solution is dried over magnesium sulfate, filtered, and the solvent is evaporated. The resulting enone **B** is dissolved in sufficient dimethylformamide to give a 0.1 to 10 0.5 molar solution. It is treated with 2 equivalents of 1-(tetrahydropyranyl)-2-iodoimidazole, 0.1 equivalents of Pd(OAc)₂, 0.2 equivalents of triphenylphosphine, and 2 equivalents of triethylamine. The mixture is heated to 90 degrees for 12 hours, then cooled to room temperature. The 15 resulting mixture is partitioned between ethyl acetate and water. The organic phase is dried over magnesium sulfate, filtered, and the solvent evaporated at reduced pressure. The product **C** is purified by chromatography on silica gel. The purified **C** is dissolved in methanol to a concentration of 0.1 to 0.5 molar and treated with 0.05 wt% of 10% palladium on carbon. It is shaken under 50 psi of hydrogen pressure for 12 hours. The catalyst is removed by filtration and the solvent 20 is evaporated. The resulting product **D** is dissolved in isopropanol to a concentration of 0.1 to 0.5 molar. It is treated with 1 molar equivalent of sodium borohydride and stirred for 2 hours. The mixture is cooled in an ice bath and excess sodium borohydride is quenched by adding 3 N HCl dropwise. The mixture is partitioned between pH 7 water and ethyl acetate. The organic phase is dried (MgSO₄) and 25 filtered. The solvent is evaporated. The resulting product is dissolved in trifluoroacetic acid containing 5% water. After stirring for 6 hours the solvent is evaporated to give **F** as a trifluoroacetate salt. This salt is dissolved in dimethylformamide and treated with 4 equivalents of 30 triethylamine, 2 equivalents of HOBt, 1 equivalent of the acid 35

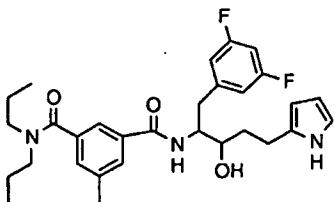
G, and 1 equivalent of EDC. After stirring overnight the mixture is partitioned between ethyl acetate and water. The organic phase is washed with 3 N aqueous sodium hydroxide solution. The organic phase is dried (MgSO_4) and the solvent is evaporated at reduced pressure. The product H is isolated by reverse phase HPLC eluting with a gradient of 100% to 0% water in acetonitrile maintaining 0.1% TFA in the eluent throughout.

The following compounds are prepared essentially according to the procedures described in the schemes, charts, examples and preparations set forth herein.

Compd.
No.

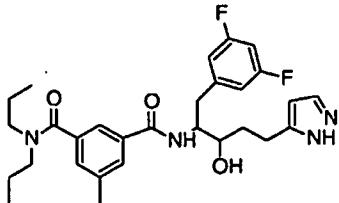
Structure/Name

4



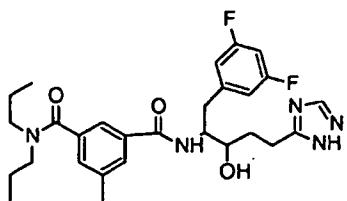
N' - [1 - (3,5-difluorobenzyl) - 2 - hydroxy - 4 - (1*H* - pyrrol - 2 - yl)butyl] - 5 - methyl - *N,N* - dipropylisophthalamide

5



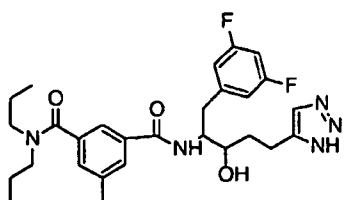
N' - [1 - (3,5-difluorobenzyl) - 2 - hydroxy - 4 - (1*H* - pyrazol - 5 - yl)butyl] - 5 - methyl - *N,N* - dipropylisophthalamide

6



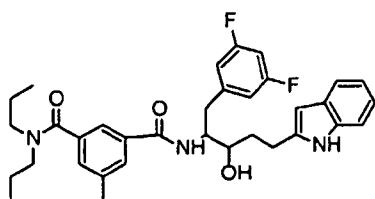
N' - [1 - (3, 5 - difluorobenzyl) - 2 - hydroxy - 4 - (1*H* - 1, 2, 4 - triazol - 5 - yl) butyl] - 5 - methyl - *N, N* - dipropylisophthalamide

7



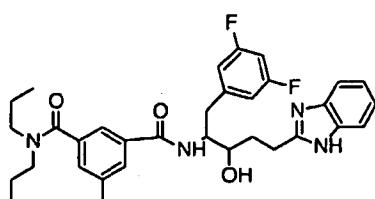
N' - [1 - (3, 5 - difluorobenzyl) - 2 - hydroxy - 4 - (1*H* - 1, 2, 3 - triazol - 5 - yl) butyl] - 5 - methyl - *N, N* - dipropylisophthalamide

8



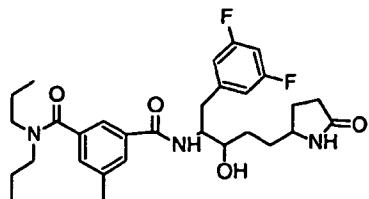
N' - [1 - (3, 5 - difluorobenzyl) - 2 - hydroxy - 4 - (1*H* - indol - 2 - yl) butyl] - 5 - methyl - *N, N* - dipropylisophthalamide

9



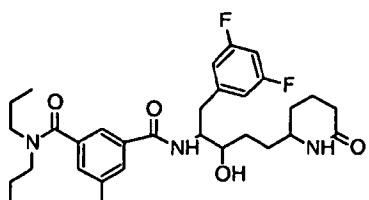
N' - [4 - (1*H* - benzimidazol - 2 - yl) - 1 - (3, 5 - difluorobenzyl) - 2 - hydroxybutyl] - 5 - methyl - *N, N* - dipropylisophthalamide

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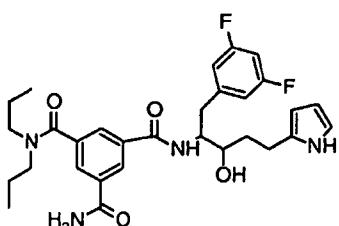
N' - [1 - (3,5-difluorobenzyl) - 2-hydroxy - 4 - (5-oxopyrrolidin-2-yl)butyl] - 5-methyl-*N,N*-dipropylisophthalamide

11



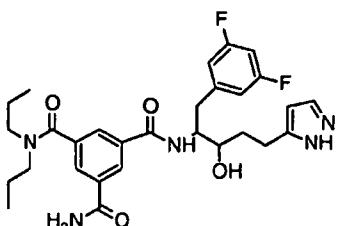
N' - [1 - (3,5-difluorobenzyl) - 2-hydroxy - 4 - (6-oxopiperidin-2-yl)butyl] - 5-methyl-*N,N*-dipropylisophthalamide

12



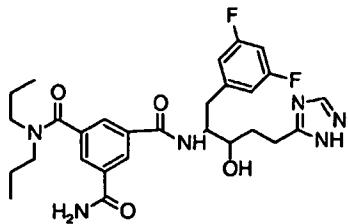
*N*³ - [1 - (3,5-difluorobenzyl) - 2-hydroxy - 4 - (1*H*-pyrrol-2-yl)butyl] - *N*¹,*N*¹-dipropylbenzene-1,3,5-tricarboxamide

13



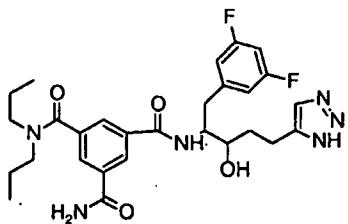
*N*³ - [1 - (3,5-difluorobenzyl) - 2-hydroxy - 4 - (1*H*-pyrazol-5-yl)butyl] - *N*¹,*N*¹-dipropylbenzene-1,3,5-tricarboxamide

14



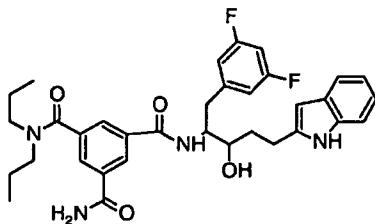
*N*³-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-1,2,4-triazol-5-yl)butyl]-*N*¹,*N*¹-dipropylbenzene-1,3,5-tricarboxamide

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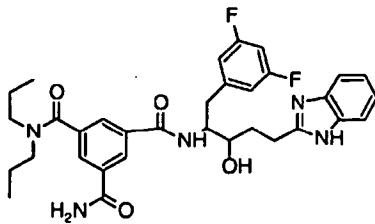
*N*³-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-1,2,3-triazol-5-yl)butyl]-*N*¹,*N*¹-dipropylbenzene-1,3,5-tricarboxamide

16



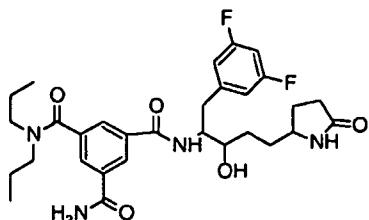
*N*³-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-indol-2-yl)butyl]-*N*¹,*N*¹-dipropylbenzene-1,3,5-tricarboxamide

17



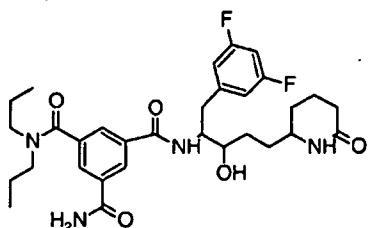
*N*³-[4-(1*H*-benzimidazol-2-yl)-1-(3,5-difluorobenzyl)-2-hydroxybutyl]-*N*¹,*N*¹-dipropylbenzene-1,3,5-tricarboxamide

18



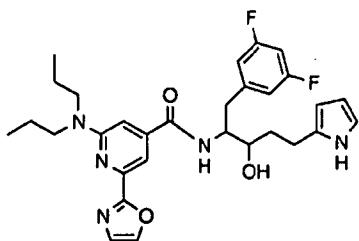
*N*³-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(5-oxopyrrolidin-2-yl)butyl]-*N*¹,*N*¹-dipropylbenzene-1,3,5-tricarboxamide

19



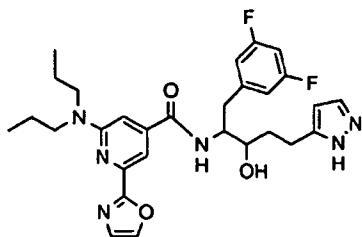
*N*³-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(6-oxopiperidin-2-yl)butyl]-*N*¹,*N*¹-dipropylbenzene-1,3,5-tricarboxamide.

20



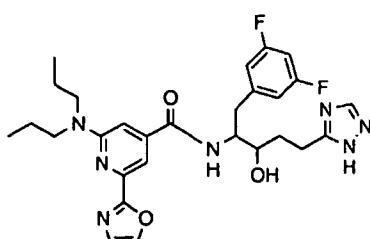
N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-pyrrol-2-yl)butyl]-2-(dipropylamino)-6-(1,3-oxazol-2-yl)isonicotinamide

21



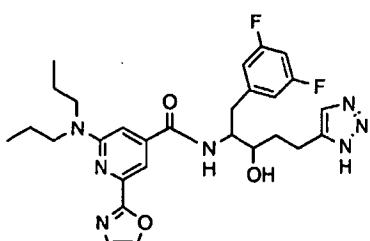
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22



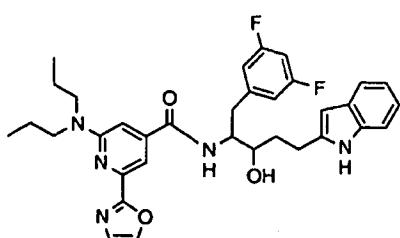
N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-1,2,4-triazol-5-yl)butyl]-2-(dipropylamino)-6-(1,3-oxazol-2-yl)isonicotinamide

23



N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-1,2,3-triazol-5-yl)butyl]-2-(dipropylamino)-6-(1,3-oxazol-2-yl)isonicotinamide

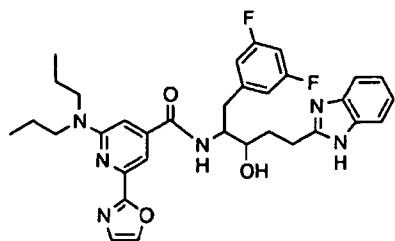
24



N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-indol-2-

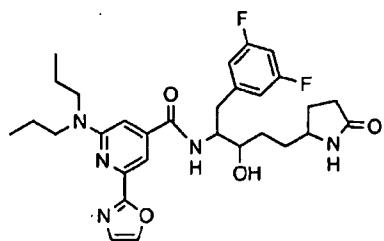
yl)butyl]-2-(dipropylamino)-6-(1,3-oxazol-2-yl)isonicotinamide

25



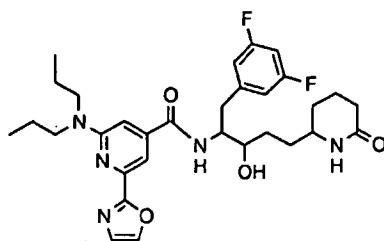
N-[4-(1*H*-benzimidazol-2-yl)-1-(3,5-difluorobenzyl)-2-hydroxybutyl]-2-(dipropylamino)-6-(1,3-oxazol-2-yl)isonicotinamide

26



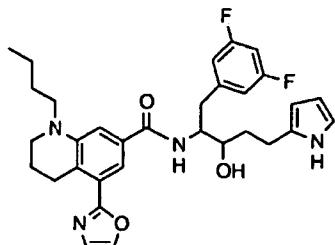
N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(5-oxopyrrolidin-2-yl)butyl]-2-(dipropylamino)-6-(1,3-oxazol-2-yl)isonicotinamide

27



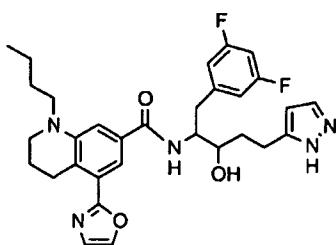
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28



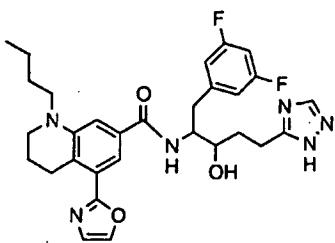
1-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-pyrrol-2-yl)butyl]-5-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoline-7-carboxamide

29



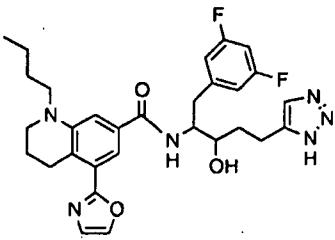
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30



1-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*,2,4-triazol-5-yl)butyl]-5-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoline-7-carboxamide

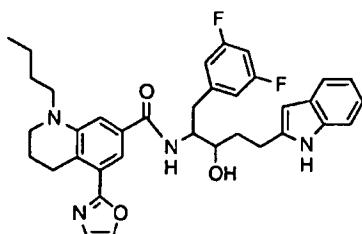
31



1-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-pyrazol-4-yl)butyl]-5-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoline-7-carboxamide

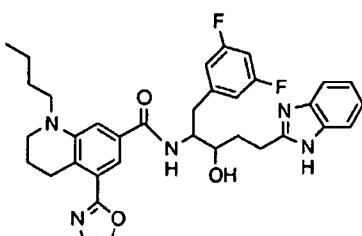
1,2,3-triazol-5-yl)butyl]-5-(1,3-oxazol-2-yl)-
1,2,3,4-tetrahydroquinoline-7-carboxamide

32



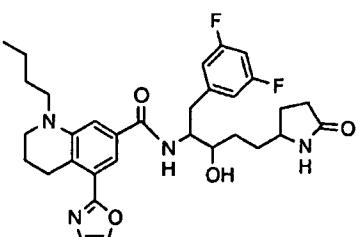
1-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1H-indol-2-yl)butyl]-5-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoline-7-carboxamide

33



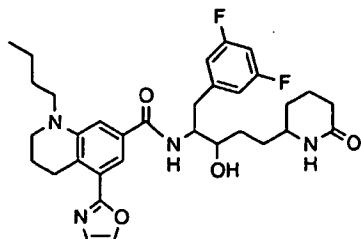
N-[4-(1*H*-benzimidazol-2-yl)-1-(3,5-difluorobenzyl)-2-hydroxybutyl]-1-butyl-5-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoline-7-carboxamide

34



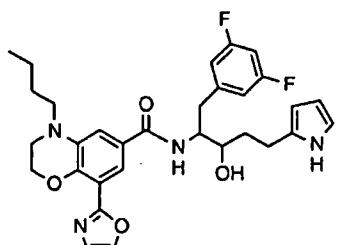
1-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(5-oxopyrrolidin-2-yl)butyl]-5-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoline-7-carboxamide

35



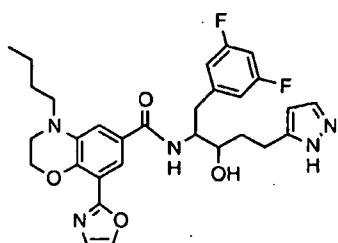
1-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(6-oxopiperidin-2-yl)butyl]-5-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoline-7-carboxamide

36



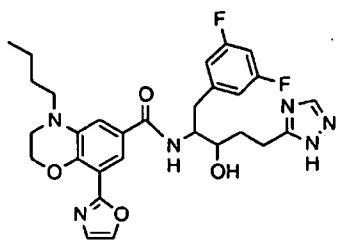
4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1H-pyrrol-2-yl)butyl]-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide

37



4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1H-pyrazol-5-yl)butyl]-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide

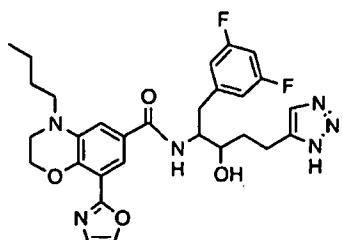
38



4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1H-

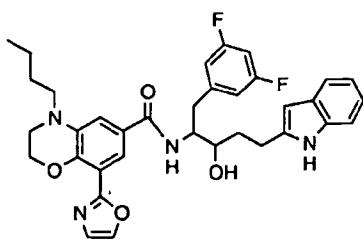
1,2,4-triazol-5-yl)butyl]-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide

39



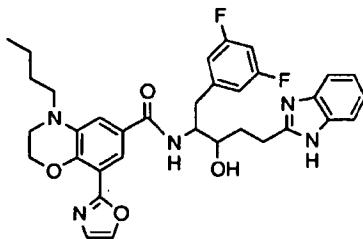
4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1H-1,2,3-triazol-5-yl)butyl]-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide

40



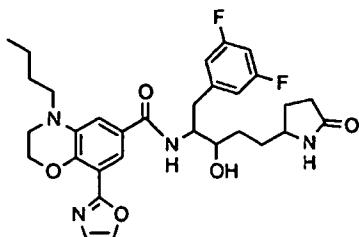
4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1H-indol-2-yl)butyl]-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide

41



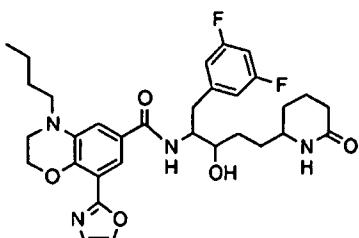
N-[4-(1H-benzimidazol-2-yl)-1-(3,5-difluorobenzyl)-2-hydroxybutyl]-4-butyl-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide

42



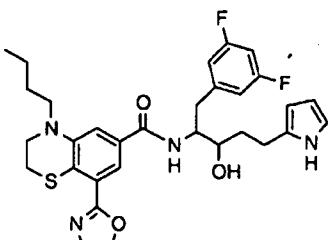
4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(5-oxopyrrolidin-2-yl)butyl]-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide

43



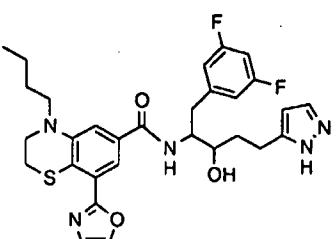
4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(6-oxopiperidin-2-yl)butyl]-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide

44



4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1H-pyrrol-2-yl)butyl]-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide

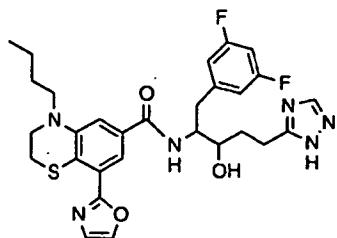
45



4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1H-

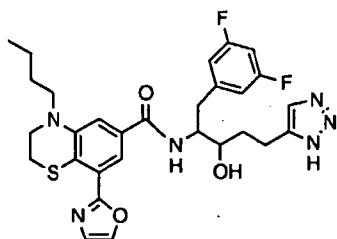
pyrazol-5-yl)butyl]-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide

46



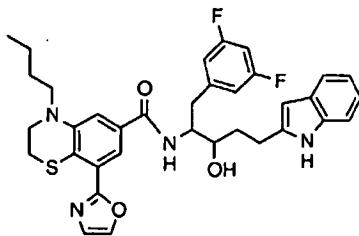
4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1H-1,2,4-triazol-5-yl)butyl]-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide

47



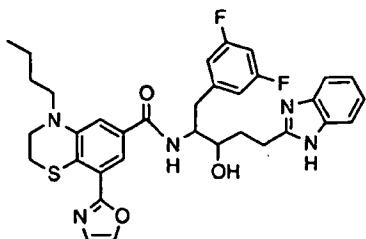
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48



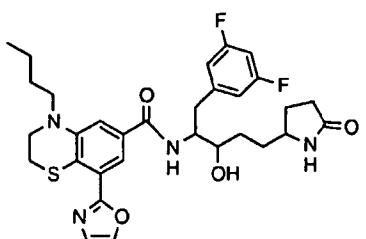
4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1H-indol-2-yl)butyl]-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide

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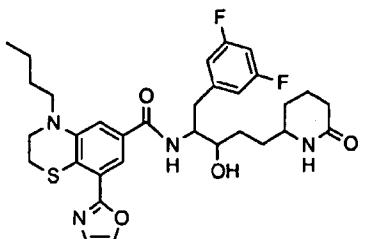
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50



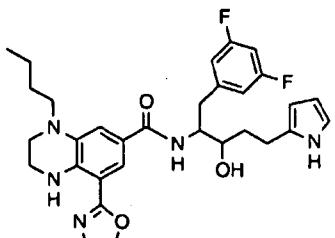
4-butyl-*N*-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(5-oxopyrrolidin-2-yl)butyl]-8-(1,3-oxazol-2-yl)-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxamide

51



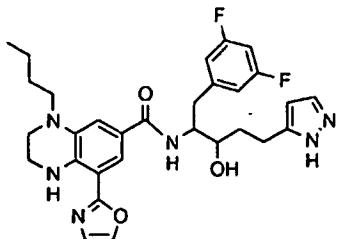
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52



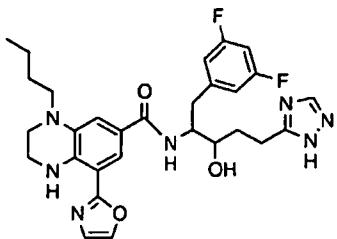
4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-pyrrol-2-yl)butyl]-8-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoxaline-6-carboxamide

53



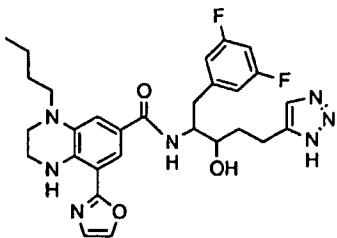
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54



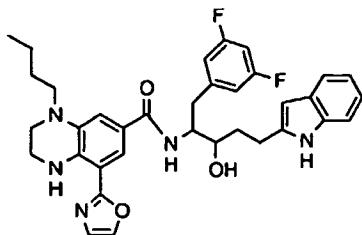
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55



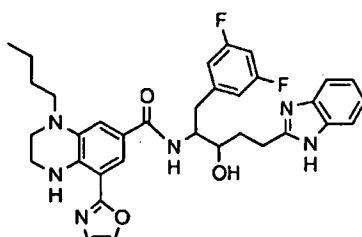
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56



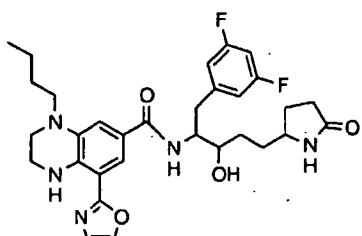
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57



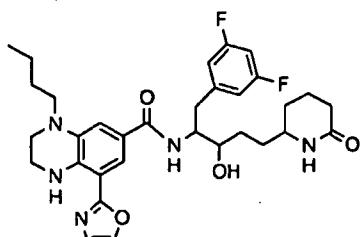
N-[4-(1H-benzimidazol-2-yl)-1-(3,5-difluorobenzyl)-2-hydroxybutyl]-4-butyl-8-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoxaline-6-carboxamide

58



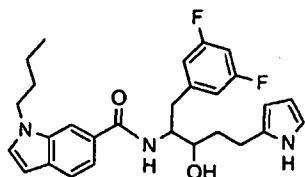
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59



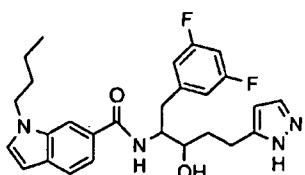
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60



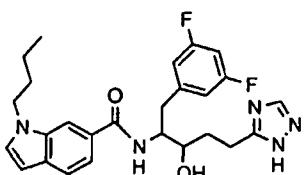
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61



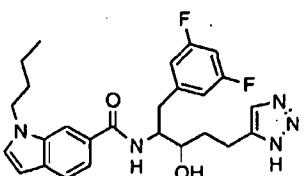
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62



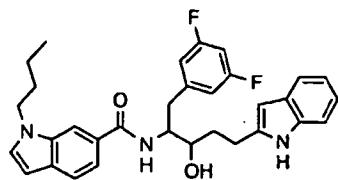
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63



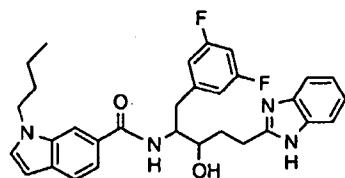
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64



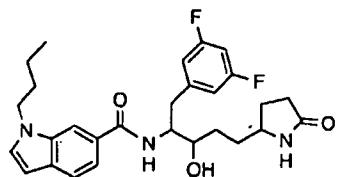
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65



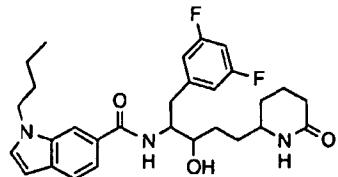
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66



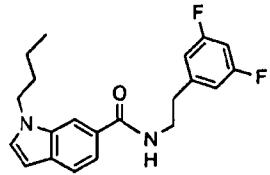
1-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(5-oxopyrrolidin-2-yl)butyl]-1H-indole-6-carboxamide

67



1-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(6-oxopiperidin-2-yl)butyl]-1H-indole-6-carboxamide

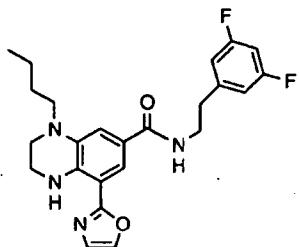
68



1-butyl-N-[2-(3,5-difluorophenyl)ethyl]-1H-indole-

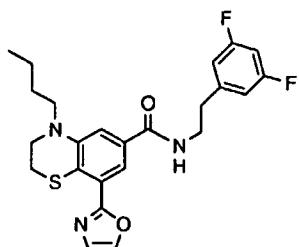
6-carboxamide

69



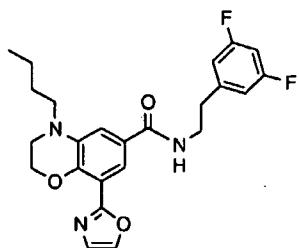
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70



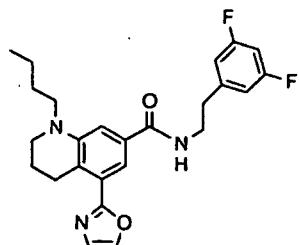
4-butyl-N-[2-(3,5-difluorophenyl)ethyl]-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide

71



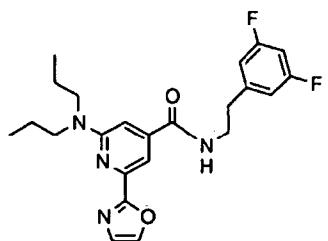
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72



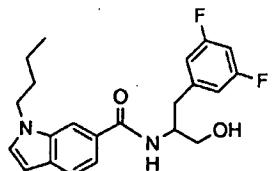
1-butyl-N-[2-(3,5-difluorophenyl)ethyl]-5-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoline-7-carboxamide

73



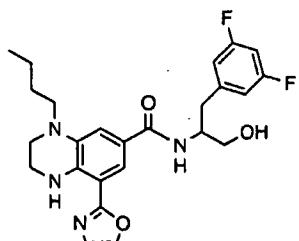
N-[2-(3,5-difluorophenyl)ethyl]-2-(dipropylamino)-6-(1,3-oxazol-2-yl)isonicotinamide

74



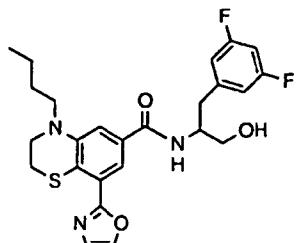
1-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxyethyl]-1H-indole-6-carboxamide

75



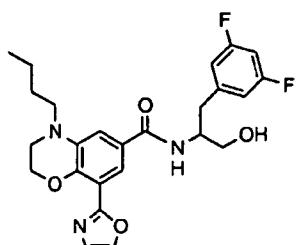
4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxyethyl]-8-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoxaline-6-carboxamide

76



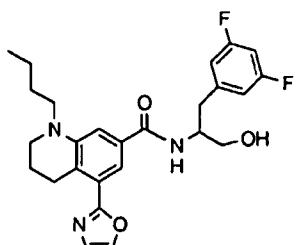
4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxyethyl]-
8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-
benzothiazine-6-carboxamide

77



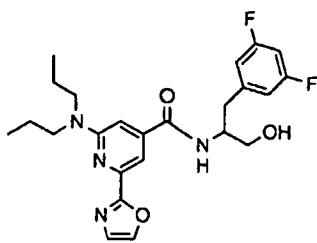
4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxyethyl]-
8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-
benzoxazine-6-carboxamide

78



1-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxyethyl]-
5-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoline-7-
carboxamide

79



N-[1-(3,5-difluorobenzyl)-2-hydroxyethyl]-2-

(dipropylamino)-6-(1,3-oxazol-2-yl)isonicotinamide

BIOLOGY EXAMPLESExample AEnzyme Inhibition Assay

5 The compounds of the invention are analyzed for inhibitory activity by use of the MBP-C125 assay. This assay determines the relative inhibition of beta-secretase cleavage of a model APP substrate, MBP-C125SW, by the compounds assayed as compared with an untreated control. A detailed description of the assay 10 parameters can be found, for example, in U.S. Patent No. 5,942,400. Briefly, the substrate is a fusion peptide formed of maltose binding protein (MBP) and the carboxy terminal 125 amino acids of APP-SW, the Swedish mutation. The beta-secretase enzyme is derived from human brain tissue as 15 described in Sinha et al, 1999, *Nature* 40:537-540) or recombinantly produced as the full-length enzyme (amino acids 1-501), and can be prepared, for example, from 293 cells expressing the recombinant cDNA, as described in WO00/47618.

20 Inhibition of the enzyme is analyzed, for example, by immunoassay of the enzyme's cleavage products. One exemplary ELISA uses an anti-MBP capture antibody that is deposited on precoated and blocked 96-well high binding plates, followed by incubation with diluted enzyme reaction supernatant, incubation with a specific reporter antibody, for example, biotinylated 25 anti-SW192 reporter antibody, and further incubation with streptavidin/alkaline phosphatase. In the assay, cleavage of the intact MBP-C125SW fusion protein results in the generation of a truncated amino-terminal fragment, exposing a new SW-192 antibody-positive epitope at the carboxy terminus. Detection 30 is effected by a fluorescent substrate signal on cleavage by the phosphatase. ELISA only detects cleavage following Leu 596 at the substrate's APP-SW 751 mutation site.

Specific Assay Procedure:

Compounds are diluted in a 1:1 dilution series to a six-point concentration curve (two wells per concentration) in one 96-plate row per compound tested. Each of the test compounds 5 is prepared in DMSO to make up a 10 millimolar stock solution. The stock solution is serially diluted in DMSO to obtain a final compound concentration of 200 micromolar at the high point of a 6-point dilution curve. Ten (10) microliters of each dilution is added to each of two wells on row C of a 10 corresponding V-bottom plate to which 190 microliters of 52 millimolar NaOAc, 7.9% DMSO, pH 4.5 are pre-added. The NaOAc 15 diluted compound plate is spun down to pellet precipitant and 20 microliters/well is transferred to a corresponding flat-bottom plate to which 30 microliters of ice-cold enzyme-substrate mixture (2.5 microliters MBP-C125SW substrate, 0.03 microliters enzyme and 24.5 microliters ice cold 0.09% TX100 per 30 microliters) is added. The final reaction mixture of 200 micromolar compound at the highest curve point is in 5% DMSO, 20 millimolar NaOAc, 0.06% TX100, at pH 4.5.

20 Warming the plates to 37 degrees C starts the enzyme reaction. After 90 minutes at 37 degrees C, 200 microliters/well cold specimen diluent is added to stop the reaction and 20 microliters/well was transferred to a 25 corresponding anti-MBP antibody coated ELISA plate for capture, containing 80 microliters/well specimen diluent. This reaction is incubated overnight at 4 degrees C and the ELISA is developed the next day after a 2 hour incubation with anti-192SW antibody, followed by Streptavidin-AP conjugate and 30 fluorescent substrate. The signal is read on a fluorescent plate reader.

Relative compound inhibition potency is determined by calculating the concentration of compound that showed a fifty percent reduction in detected signal (IC_{50}) compared to the enzyme reaction signal in the control wells with no added

compound. In this assay, preferred compounds of the invention exhibit an IC₅₀ of less than 50 micromolar.

Example B

5 Cell Free Inhibition Assay Utilizing a Synthetic APP Substrate

A synthetic APP substrate that can be cleaved by beta-secretase and having N-terminal biotin and made fluorescent by the covalent attachment of Oregon green at the Cys residue is 10 used to assay beta-secretase activity in the presence or absence of the inhibitory compounds of the invention. Useful substrates include the following:

15 Biotin-SEVNL-DAEFRC[oregon green]KK [SEQ ID NO:
1] Biotin-SEVKM-DAEFRC[oregon green]KK [SEQ ID NO:
2] Biotin-GLNIKTEEISEISY-EVEFRC[oregon green]KK [SEQ ID NO:
3] Biotin-ADRGGLTTRPGSGLTNIKTEEISEVNL-DAEFRC[oregon green]KK
[SEQ ID NO:4] Biotin-FVNQHLCoxGSHLVEALY-LVCoxGERGFFYTPKAC[oregon
green]KK [SEQ ID NO: 5]

The enzyme (0.1 nanomolar) and test compounds (0.001 - 100 25 micromolar) are incubated in pre-blocked, low affinity, black plates (384 well) at 37 degrees for 30 minutes. The reaction is initiated by addition of 150 millimolar substrate to a final volume of 30 microliter per well. The final assay conditions are: 0.001 - 100 micromolar compound inhibitor; 0.1 molar 30 sodium acetate (pH 4.5); 150 nanomolar substrate; 0.1 nanomolar soluble beta-secretase; 0.001% Tween 20, and 2% DMSO. The assay mixture is incubated for 3 hours at 37 degrees C, and the reaction is terminated by the addition of a saturating concentration of immunopure streptavidin. After incubation 35 with streptavidin at room temperature for 15 minutes,

fluorescence polarization is measured, for example, using a L JL Acquirest (Ex485 nm/ Em530 nm). The activity of the beta-secretase enzyme is detected by changes in the fluorescence polarization that occur when the substrate is cleaved by the 5 enzyme. Incubation in the presence or absence of compound inhibitor demonstrates specific inhibition of beta-secretase enzymatic cleavage of its synthetic APP substrate. In this assay, preferred compounds of the invention exhibit an IC₅₀ of less than 50 micromolar.

10

Example C**Beta-Secretase Inhibition: P26-P4' SW Assay**

Synthetic substrates containing the beta-secretase cleavage site of APP are used to assay beta-secretase activity, 15 using the methods described, for example, in published PCT application WO00/47618. The P26-P4' SW substrate is a peptide of the sequence:

(biotin)CGGADRGGLTTRPGSGLTNIKTEEISEVNLDLAEF [SEQ ID NO: 6]

The P26-P1 standard has the sequence:
20 (biotin)CGGADRGGLTTRPGSGLTNIKTEEISEVNL [SEQ ID NO: 7].

Briefly, the biotin-coupled synthetic substrates are incubated at a concentration of from about 0 to about 200 micromolar in this assay. When testing inhibitory compounds, a substrate concentration of about 1.0 micromolar is preferred. 25 Test compounds diluted in DMSO are added to the reaction mixture, with a final DMSO concentration of 5%. Controls also contain a final DMSO concentration of 5%. The concentration of beta secretase enzyme in the reaction is varied, to give product concentrations with the linear range of the ELISA 30 assay, about 125 to 2000 picomolar, after dilution.

The reaction mixture also includes 20 millimolar sodium acetate, pH 4.5, 0.06% Triton X100, and is incubated at 37 degrees C for about 1 to 3 hours. Samples are then diluted in assay buffer (for example, 145.4 nanomolar sodium chloride, 35 9.51 millimolar sodium phosphate, 7.7 millimolar sodium azide,

0.05% Triton X405, 6g/liter bovine serum albumin, pH 7.4) to quench the reaction, then diluted further for immunoassay of the cleavage products.

Cleavage products can be assayed by ELISA. Diluted 5 samples and standards are incubated in assay plates coated with capture antibody, for example, SW192, for about 24 hours at 4 degrees C. After washing in TTBS buffer (150 millimolar sodium chloride, 25 millimolar Tris, 0.05% Tween 20, pH 7.5), the samples are incubated with streptavidin-AP according to the 10 manufacturer's instructions. After a one hour incubation at room temperature, the samples are washed in TTBS and incubated with fluorescent substrate solution A (31.2 g/liter 2-amino-2-methyl-1-propanol, 30 mg/liter, pH 9.5). Reaction with 15 streptavidin-alkaline phosphate permits detection by fluorescence. Compounds that are effective inhibitors of beta-secretase activity demonstrate reduced cleavage of the substrate as compared to a control.

Example D

20 **Assays using Synthetic Oligopeptide-Substrates**

Synthetic oligopeptides are prepared that incorporate the known cleavage site of beta-secretase, and optionally detectable tags, such as fluorescent or chromogenic moieties. Examples of such peptides, as well as their production and 25 detection methods are described in U.S. Patent No: 5,942,400, herein incorporated by reference. Cleavage products can be detected using high performance liquid chromatography, or fluorescent or chromogenic detection methods appropriate to the peptide to be detected, according to methods well known in the 30 art.

By way of example, one such peptide has the sequence SEVNL-DAEF [SEQ ID NO: 8], and the cleavage site is between residues 5 and 6. Another preferred substrate has the sequence ADRGLTTRPGSGLTNIKTEEISEVNL-DAEF [SEQ ID NO: 9], and the 35 cleavage site is between residues 26 and 27.

These synthetic APP substrates are incubated in the presence of beta-secretase under conditions sufficient to result in beta-secretase mediated cleavage of the substrate. Comparison of the cleavage results in the presence of the 5 compound inhibitor to control results provides a measure of the compound's inhibitory activity.

Example E

Inhibition of Beta-Secretase Activity - Cellular Assay

10 An exemplary assay for the analysis of inhibition of beta-secretase activity utilizes the human embryonic kidney cell line HEKp293 (ATCC Accession No. CRL-1573) transfected with APP751 containing the naturally occurring double mutation Lys651Met52 to Asn651Leu652 (numbered for APP751), commonly 15 called the Swedish mutation and shown to overproduce A beta (Citron et al., 1992, *Nature* 360:672-674), as described in U.S. Patent No. 5,604,102.

20 The cells are incubated in the presence/absence of the inhibitory compound (diluted in DMSO) at the desired concentration, generally up to 10 micrograms/ml. At the end of the treatment period, conditioned media is analyzed for beta-secretase activity, for example, by analysis of cleavage fragments. A beta can be analyzed by immunoassay, using 25 specific detection antibodies. The enzymatic activity is measured in the presence and absence of the compound inhibitors to demonstrate specific inhibition of beta-secretase mediated cleavage of APP substrate.

Example F

Inhibition of Beta-Secretase in Animal Models of AD

30 Various animal models can be used to screen for inhibition of beta-secretase activity. Examples of animal models useful in the invention include, but are not limited to, mouse, guinea pig, dog, and the like. The animals used can be wild type, 35 transgenic, or knockout models. In addition, mammalian models

can express mutations in APP, such as APP695-SW and the like described herein. Examples of transgenic non-human mammalian models are described in U.S. Patent Nos. 5,604,102, 5,912,410 and 5,811,633.

5 PDAPP mice, prepared as described in Games et al., 1995, *Nature* 373:523-527 are useful to analyze *in vivo* suppression of A beta release in the presence of putative inhibitory compounds. As described in U.S. Patent No. 6,191,166, 4 month old PDAPP mice are administered compound formulated in vehicle, 10 such as corn oil. The mice are dosed with compound (1-30 mg/ml; preferably 1-10 mg/ml). After time, e.g., 3-10 hours, the animals are sacrificed, and brains removed for analysis.

Transgenic animals are administered an amount of the compound inhibitor formulated in a carrier suitable for the 15 chosen mode of administration. Control animals are untreated, treated with vehicle, or treated with an inactive compound. Administration can be acute, i.e., single dose or multiple doses in one day, or can be chronic, i.e., dosing is repeated daily for a period of days. Beginning at time 0, brain tissue 20 or cerebral fluid is obtained from selected animals and analyzed for the presence of APP cleavage peptides, including A beta, for example, by immunoassay using specific antibodies for A beta detection. At the end of the test period, animals are sacrificed and brain tissue or cerebral fluid is analyzed for 25 the presence of A beta and/or beta-amyloid plaques. The tissue is also analyzed for necrosis.

Animals administered the compound inhibitors of the invention are expected to demonstrate reduced A beta in brain tissues or cerebral fluids and reduced beta amyloid plaques in 30 brain tissue, as compared with non-treated controls.

Example G

Inhibition of A Beta Production in Human Patients

Patients suffering from Alzheimer's Disease (AD) 35 demonstrate an increased amount of A beta in the brain. AD

patients are administered an amount of the compound inhibitor formulated in a carrier suitable for the chosen mode of administration. Administration is repeated daily for the duration of the test period. Beginning on day 0, cognitive and 5 memory tests are performed, for example, once per month.

Patients administered the compound inhibitors are expected to demonstrate slowing or stabilization of disease progression as analyzed by changes in one or more of the following disease parameters: A beta present in CSF or plasma; brain or 10 hippocampal volume; A beta deposits in the brain; amyloid plaque in the brain; and scores for cognitive and memory function, as compared with control, non-treated patients.

Example H

15 **Prevention of A Beta Production in Patients at Risk for AD**

Patients predisposed or at risk for developing AD are identified either by recognition of a familial inheritance pattern, for example, presence of the Swedish Mutation, and/or by monitoring diagnostic parameters. Patients identified as 20 predisposed or at risk for developing AD are administered an amount of the compound inhibitor formulated in a carrier suitable for the chosen mode of administration. Administration is repeated daily for the duration of the test period. Beginning on day 0, cognitive and memory tests are performed, 25 for example, once per month.

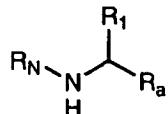
Patients administered the compound inhibitors are expected to demonstrate slowing or stabilization of disease progression as analyzed by changes in one or more of the following disease parameters: A beta present in CSF or plasma; brain or 30 hippocampal volume; amyloid plaque in the brain; and scores for cognitive and memory function, as compared with control, non-treated patients.

35 The invention has been described with reference to various specific and preferred embodiments and techniques. However, it

should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

What is claimed is:

1. A compound of the formula I:



(I)

5

or a pharmaceutically acceptable salt thereof, wherein

R₁ is -(CH₂)₁₋₂-S(O)₀₋₂-(C₁-C₆ alkyl), or

10 C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, =O, -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino, -N(R)C(O)R'-, -OC(=O)-amino and -OC(=O)-mono- or dialkylamino, or

15 C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, and mono- or dialkylamino, or

20 aryl, heteroaryl, heterocyclyl, aryl-(C₁-C₆)alkyl-, heteroaryl-(C₁-C₆)alkyl-, or heterocyclyl-(C₁-C₆)alkyl-, where the ring portions of each are optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, -OH, -SH, -C≡N, -NO₂, -NR₁₀₅R'₁₀₅, -CO₂R, -N(R)COR', -N(R)SO₂R', -C(=O)-(C₁-C₄) alkyl, -SO₂-amino, -SO₂-monoalkylamino, -SO₂-dialkylamino, -C(=O)-amino, -C(=O)-monoalkylamino, -C(=O)-dialkylamino, -SO₂-(C₁-C₄) alkyl,

25 C₁-C₆ alkoxy optionally substituted with 1, 2, or 3 groups which are independently selected from halogen,

30 C₃-C₇ cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -

OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, -C₁-C₆ alkyl and mono- or dialkylamino,

5 C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, mono- or dialkylamino and -C₁-C₃ alkyl, and

10 C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, C₁-C₆ alkyl and mono- or dialkylamino; and the heterocyclyl group is optionally further substituted with oxo;

R and R' independently are hydrogen, C₁-C₁₀ alkyl, C₁-C₁₀ alkylaryl or C₁-C₁₀ alkylheteroaryl;

15 R_N is R'₁₀₀, -SO₂R'₁₀₀, -(CRR')₁₋₆R'₁₀₀, -C(=O)-(CRR')₀₋₆R₁₀₀, -C(=O)-(CRR')₁₋₆-O-R'₁₀₀, -C(=O)-(CRR')₁₋₆-S-R'₁₀₀, -C(=O)-(CRR')₁₋₆-C(=O)-R₁₀₀, -C(=O)-(CRR')₁₋₆-SO₂-R₁₀₀ or -C(=O)-(CRR')₁₋₆-NR₁₀₀-R'₁₀₀;

20 R₁₀₀ and R'₁₀₀ independently represent aryl, heteroaryl, heterocyclyl, -aryl-W-aryl, -aryl-W-heteroaryl, -aryl-W-heterocyclyl, -heteroaryl-W-aryl, -heteroaryl-W-heteroaryl, -heteroaryl-W-heterocyclyl, -heterocyclyl-W-aryl, -heterocyclyl-W-heteroaryl, -heterocyclyl, -CH[(CH₂)₀₋₂-O-R₁₅₀]-(CH₂)₀₋₂-aryl, -CH[(CH₂)₀₋₂-O-R₁₅₀]-(CH₂)₀₋₂-heterocyclyl or -CH[(CH₂)₀₋₂-O-R₁₅₀]-(CH₂)₀₋₂-heteroaryl, where the ring portions of each are optionally substituted with 1, 2, or 3 groups independently selected from

25 -OR, -NO₂, C₁-C₆ alkyl, halogen, -C≡N, -OCF₃, -CF₃, -(CH₂)₀₋₄-O-P(=O)(OR)(OR'), -(CH₂)₀₋₄-CO-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-O-(CH₂)₀₋₄-CONR₁₀₂R'₁₀₂, -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl), -(CH₂)₀₋₄-CO-(CH₂)₀₋₄(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-R₁₁₀,

30 -(CH₂)₀₋₄-R₁₂₀, -(CH₂)₀₋₄-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₁₀, -(CH₂)₀₋₄-

35

CO-R₁₂₀, -(CH₂)₀₋₄-CO-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₄₀, -(CH₂)₀₋₄-CO-
 O-R₁₅₀, -(CH₂)₀₋₄-SO₂-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-SO-(C₁-C₈
 alkyl), -(CH₂)₀₋₄-SO₂-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-SO₂-
 (CH₂)₀₋₄-(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-N(R₁₅₀)-CO-O-R₁₅₀,
 5 -(CH₂)₀₋₄-N(R₁₅₀)-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CS-
 N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CO-R₁₀₅, -(CH₂)₀₋₄-NR₁₀₅R'₁₀₅,
 -(CH₂)₀₋₄-R₁₄₀, -(CH₂)₀₋₄-O-CO-(C₁-C₆ alkyl), -(CH₂)₀₋₄-O-
 P(O)-(O-R₁₁₀)₂, -(CH₂)₀₋₄-O-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-O-CS-
 N(R₁₅₀)₂, -(CH₂)₀₋₄-O-(R₁₅₀), -(CH₂)₀₋₄-O-R₁₅₀'-COOH, -
 10 -(CH₂)₀₋₄-S-(R₁₅₀), -(CH₂)₀₋₄-N(R₁₅₀)-SO₂-R₁₀₅, -(CH₂)₀₋₄-
 C₃-C₇ cycloalkyl, (C₂-C₁₀) alkenyl, and (C₂-
 C₁₀) alkynyl, or

R₁₀₀ is C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 R₁₁₅
 groups, or

15 R₁₀₀ is -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl) or -(C₁-C₆ alkyl)-S-(C₁-C₆
 alkyl), each of which is optionally substituted with 1, 2, .
 or 3 R₁₁₅ groups, or

R₁₀₀ is C₃-C₈ cycloalkyl optionally substituted with 1, 2, or 3
 R₁₁₅ groups;

20 W is -(CH₂)₀₋₄-, -O-, -S(O)₀₋₂₋, -N(R₁₃₅)-, -CR(OH)- or -C(O)-;
 R₁₀₂ and R₁₀₂' independently are hydrogen, or
 C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups
 that are independently halogen, aryl or -R₁₁₀;

25 R₁₀₅ and R'₁₀₅ independently represent -H, -R₁₁₀, -R₁₂₀, C₃-C₇
 cycloalkyl, -(C₁-C₂ alkyl)-(C₃-C₇ cycloalkyl), -(C₁-C₆
 alkyl)-O-(C₁-C₃ alkyl), C₂-C₆ alkenyl, C₂-C₆ alkynyl, or C₁-
 C₆ alkyl chain with one double bond and one triple bond,
 or

C₁-C₆ alkyl optionally substituted with -OH or -NH₂; or,

30 C₁-C₆ alkyl optionally substituted with 1, 2, or 3 groups
 independently selected from halogen, or

R₁₀₅ and R'₁₀₅ together with the atom to which they are attached
 form a 3 to 7 membered carbocyclic ring, where one member
 is optionally a heteratom selected from -O-, -S(O)₀₋₂₋, -

N(R₁₃₅)-, the ring being optionally substituted with 1, 2 or 3 independently selected R₁₄₀ groups;

R₁₁₅ at each occurrence is independently halogen, -OH, -CO₂R₁₀₂, -C₁-C₆ thioalkoxy, -CO₂-phenyl, -NR₁₀₅R'₁₃₅, -SO₂-(C₁-C₈ alkyl), -C(=O)R₁₈₀, R₁₈₀, -CONR₁₀₅R'₁₀₅, -SO₂NR₁₀₅R'₁₀₅, -NH-CO-(C₁-C₆ alkyl), -NH-C(=O)-OH, -NH-C(=O)-OR, -NH-C(=O)-O-phenyl, -O-C(=O)-(C₁-C₆ alkyl), -O-C(=O)-amino, -O-C(=O)-mono- or dialkylamino, -O-C(=O)-phenyl, -O-(C₁-C₆ alkyl)-CO₂H, -NH-SO₂-(C₁-C₆ alkyl), C₁-C₆ alkoxy or C₁-C₆ haloalkoxy;

R₁₃₅ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -(CH₂)₀₋₂-(aryl), -(CH₂)₀₋₂-(heteroaryl), or -(CH₂)₀₋₂-(heterocyclyl);

R₁₄₀ is heterocyclyl optionally substituted with 1, 2, 3, or 4 groups independently selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, amino(C₁-C₆)alkyl, mono(C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl, and =O;

R₁₅₀ is hydrogen, C₃-C₇ cycloalkyl, -(C₁-C₂ alkyl)-(C₃-C₇ cycloalkyl), C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkyl with one double bond and one triple bond, -R₁₁₀, -R₁₂₀, or C₁-C₆ alkyl optionally substituted with 1, 2, 3, or 4 groups independently selected from -OH, -NH₂, C₁-C₃ alkoxy, R₁₁₀, and halogen;

R_{150'} is C₃-C₇ cycloalkyl, -(C₁-C₃ alkyl)-(C₃-C₇ cycloalkyl), C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkyl with one double bond and one triple bond, -R₁₁₀, -R₁₂₀, or C₁-C₆ alkyl optionally substituted with 1, 2, 3, or 4 groups independently selected from -OH, -NH₂, C₁-C₃ alkoxy, R₁₁₀, and halogen;

R₁₈₀ is selected from morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S-oxide, homothiomorpholinyl S,S-

dioxide, pyrrolinyl and pyrrolidinyl, each of which is optionally substituted with 1, 2, 3, or 4 groups independently selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, amino(C₁-C₆)alkyl, mono(C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl, and =O;

5 R₁₁₀ is aryl optionally substituted with 1 or 2 R₁₂₅ groups;

10 R₁₂₅ at each occurrence is independently halogen, amino, mono- or dialkylamino, -OH, -C≡N, -SO₂-NH₂, -SO₂-NH-C₁-C₆ alkyl, -SO₂-N(C₁-C₆ alkyl)₂, -SO₂-(C₁-C₄ alkyl), -CO-NH₂, -CO-NH-C₁-C₆ alkyl, or -CO-N(C₁-C₆ alkyl)₂, or

15 C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently selected from C₁-C₃ alkyl, halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, and mono- and dialkylamino, or

20 C₁-C₆ alkoxy optionally substituted with one, two or three of halogen;

25 R₁₂₀ is heteroaryl, which is optionally substituted with 1 or 2 R₁₂₅ groups; and

R₁₃₀ is heterocyclyl optionally substituted with 1 or 2 R₁₂₅ groups; and

25 R_a represents hydrogen, hydroxymethyl, or -CH(OH)CH₂CH₂R₂, wherein R₂ is R₁₂₀ or R₁₃₀.

2. A compound according to claim 1 wherein

R₁ is aryl, heteroaryl, heterocyclyl, aryl-(C₁-C₆)alkyl-, heteroaryl-(C₁-C₆)alkyl-, or heterocyclyl-(C₁-C₆)alkyl-, where the ring portions of each are optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, -OH, -SH, -C≡N, -NO₂, -NR₁₀₅R'₁₀₅, -CO₂R, -N(R)COR', or -N(R)SO₂R',

35 -C(=O)-(C₁-C₄) alkyl, -SO₂-amino, -SO₂-mono or

dialkylamino, $-C(=O)$ -amino, $-C(=O)$ -mono or
 dialkylamino, $-SO_2-(C_1-C_4)$ alkyl, or
 C_1-C_6 alkoxy optionally substituted with 1, 2, or 3
 groups which are independently selected from
 5 halogen, or
 C_3-C_7 cycloalkyl optionally substituted with 1, 2, or
 3 groups independently selected from halogen, -
 OH , $-SH$, $-C\equiv N$, $-CF_3$, C_1-C_3 alkoxy, amino, $-C_1-C_6$
 alkyl and mono- or dialkylamino, or
 10 C_1-C_{10} alkyl optionally substituted with 1, 2, or 3
 groups independently selected from halogen, $-OH$,
 $-SH$, $-C\equiv N$, $-CF_3$, $-C_1-C_3$ alkoxy, amino, mono- or
 dialkylamino and $-C_1-C_3$ alkyl, or
 15 C_2-C_{10} alkenyl or C_2-C_{10} alkynyl each of which is
 optionally substituted with 1, 2, or 3 groups
 independently selected from halogen, $-OH$, $-SH$,
 $-C\equiv N$, $-CF_3$, C_1-C_3 alkoxy, amino, C_1-C_6 alkyl and
 mono- or dialkylamino; and the heterocyclyl
 20 group is optionally further substituted with
 oxo.

3. A compound according to claim 2 wherein
 R_N is $-C(=O)-(CR'R')_{0-6}R_{100}$;
 R_{100} represents aryl, heteroaryl, heterocyclyl, -aryl-W-aryl, -
 aryl-W-heteroaryl, -aryl-W-heterocyclyl, -heteroaryl-W-
 25 aryl, -heteroaryl-W-heteroaryl, -heteroaryl-W-
 heterocyclyl, -heterocyclyl-W-aryl, -heterocyclyl-W-
 heteroaryl, -heterocyclyl-W-heterocyclyl, $-CH[(CH_2)_{0-2}-O-$
 $R_{150}]- (CH_2)_{0-2}-aryl$, $-CH[(CH_2)_{0-2}-O-R_{150}]- (CH_2)_{0-2}-heterocyclyl$
 or $-CH[(CH_2)_{0-2}-O-R_{150}]- (CH_2)_{0-2}-heteroaryl$, where the ring
 30 portions of each are optionally substituted with 1, 2, or
 3 groups independently selected from
 $-OR$, $-NO_2$, C_1-C_6 alkyl, halogen, $-C\equiv N$, $-OCF_3$, $-CF_3$, $-(CH_2)_{0-4}-O-P(=O)(OR)(OR')$, $-(CH_2)_{0-4}-CO-NR_{105}R'_{105}$, $-(CH_2)_{0-4}-O-(CH_2)_{0-4}-CONR_{102}R'_{102}$, $-(CH_2)_{0-4}-CO-(C_1-C_{12}$ alkyl), $-(CH_2)_{0-4}-CO-(C_2-C_{12}$ alkenyl), $-(CH_2)_{0-4}-CO-(C_2-C_{12}$ alkynyl),

$-\text{CH}_2\text{O}_4\text{CO}-(\text{CH}_2)\text{O}_4(\text{C}_3\text{-C}_7\text{ cycloalkyl}),$ $-\text{CH}_2\text{O}_4\text{R}_{110},$
 $-\text{CH}_2\text{O}_4\text{R}_{120},$ $-\text{CH}_2\text{O}_4\text{R}_{130},$ $-\text{CH}_2\text{O}_4\text{CO-R}_{110},$ $-\text{CH}_2\text{O}_4\text{CO-R}_{120},$
 $-\text{CH}_2\text{O}_4\text{CO-R}_{130},$ $-\text{CH}_2\text{O}_4\text{CO-R}_{140},$ $-\text{CH}_2\text{O}_4\text{CO-O-R}_{150},$
 $-\text{CH}_2\text{O}_4\text{SO}_2\text{NR}_{105}\text{R}'_{105},$ $-\text{CH}_2\text{O}_4\text{SO-(C}_1\text{-C}_8$
5 $\text{alkyl}),$ $-\text{CH}_2\text{O}_4\text{SO}_2\text{-(C}_1\text{-C}_{12}\text{ alkyl}),$ $-\text{CH}_2\text{O}_4\text{SO}_2\text{-(CH}_2\text{O}_4\text{-(C}_3\text{-C}_7\text{ cycloalkyl}),$
 $-\text{CH}_2\text{O}_4\text{N(R}_{150}\text{)-CO-O-R}_{150},$ $-\text{CH}_2\text{O}_4\text{N(R}_{150}\text{)-CO-N(R}_{150}\text{)}_2,$ $-\text{CH}_2\text{O}_4\text{N(R}_{150}\text{)-CS-}$
 $\text{N(R}_{150}\text{)}_2,$ $-\text{CH}_2\text{O}_4\text{N(R}_{150}\text{)-CO-R}_{105},$ $-\text{CH}_2\text{O}_4\text{NR}_{105}\text{R}'_{105},$
 $-\text{CH}_2\text{O}_4\text{R}_{140},$ $-\text{CH}_2\text{O}_4\text{O-CO-(C}_1\text{-C}_6\text{ alkyl}),$ $-\text{CH}_2\text{O}_4\text{O-}$
10 $\text{P(O)-(O-R}_{110}\text{)}_2,$ $-\text{CH}_2\text{O}_4\text{O-CO-N(R}_{150}\text{)}_2,$ $-\text{CH}_2\text{O}_4\text{O-CS-}$
 $\text{N(R}_{150}\text{)}_2,$ $-\text{CH}_2\text{O}_4\text{O-(R}_{150}\text{)},$ $-\text{CH}_2\text{O}_4\text{O-R}_{150}'\text{-COOH},$ $-\text{CH}_2\text{O}_4\text{S-}$
 $\text{(R}_{150}\text{)},$ $-\text{CH}_2\text{O}_4\text{N(R}_{150}\text{)-SO}_2\text{-R}_{105},$ $-\text{CH}_2\text{O}_4\text{C}_3\text{-C}_7\text{ cycloalkyl, (C}_2\text{-C}_{10}\text{)alkenyl, or (C}_2\text{-C}_{10}\text{)alkynyl,}$
 or
15 R_{100} is $\text{C}_1\text{-C}_{10}\text{ alkyl}$ optionally substituted with 1, 2, or 3 R_{115} groups, or
 R_{100} is $-(\text{C}_1\text{-C}_6\text{ alkyl})\text{-O-C}_1\text{-C}_6\text{ alkyl}$ or $-(\text{C}_1\text{-C}_6\text{ alkyl})\text{-S-(C}_1\text{-C}_6$
 $\text{alkyl}),$ each of which is optionally substituted with 1, 2, or 3 R_{115} groups, or
20 R_{100} is $\text{C}_3\text{-C}_8\text{ cycloalkyl}$ optionally substituted with 1, 2, or 3 R_{115} groups.

4. A compound according to claim 3 wherein

R_N is $-\text{C(=O)-R}_{100}$; and

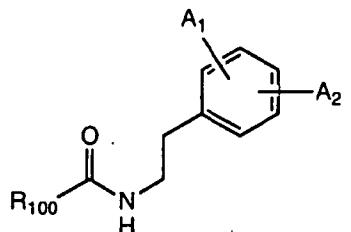
25 R_{100} represents aryl, or heteroaryl, where the ring portions of each are optionally substituted with 1, 2, or 3 groups independently selected from

$-\text{OR},$ $-\text{NO}_2,$ $\text{C}_1\text{-C}_6\text{ alkyl, halogen, -C}\equiv\text{N, -OCF}_3,$ $-\text{CF}_3,$ $-(\text{CH}_2)\text{O-}$
 $4\text{-O-P(=O)(OR)(OR')},$ $-(\text{CH}_2)\text{O}_4\text{CO-NR}_{105}\text{R}'_{105},$ $-(\text{CH}_2)\text{O}_4\text{O-}$
30 $(\text{CH}_2)\text{O}_4\text{CONR}_{102}\text{R}_{102}',$ $-(\text{CH}_2)\text{O}_4\text{CO-(C}_1\text{-C}_{12}\text{ alkyl),}$ $-(\text{CH}_2)\text{O}_4\text{CO-}$
 $(\text{C}_2\text{-C}_{12}\text{ alkenyl),}$ $-(\text{CH}_2)\text{O}_4\text{CO-(C}_2\text{-C}_{12}\text{ alkynyl),}$ $-(\text{CH}_2)\text{O}_4\text{CO-(CH}_2\text{O}_4\text{-(C}_3\text{-C}_7\text{ cycloalkyl),}$
 $-(\text{CH}_2)\text{O}_4\text{R}_{110},$ $-(\text{CH}_2)\text{O}_4\text{R}_{120},$ $-(\text{CH}_2)\text{O}_4\text{R}_{130},$ $-(\text{CH}_2)\text{O}_4\text{CO-R}_{110},$
 $-(\text{CH}_2)\text{O}_4\text{CO-R}_{120},$ $-(\text{CH}_2)\text{O}_4\text{CO-R}_{130},$ $-(\text{CH}_2)\text{O}_4\text{CO-R}_{140},$ $-(\text{CH}_2)\text{O}_4\text{CO-}$
35 $\text{O-R}_{150},$ $-(\text{CH}_2)\text{O}_4\text{SO}_2\text{NR}_{105}\text{R}'_{105},$ $-(\text{CH}_2)\text{O}_4\text{SO-(C}_1\text{-C}_8$

alkyl), $-(\text{CH}_2)_{0-4}-\text{SO}_2-(\text{C}_1-\text{C}_{12}$ alkyl), $-(\text{CH}_2)_{0-4}-\text{SO}_2-$
 $(\text{CH}_2)_{0-4}-\text{(C}_3-\text{C}_7$ cycloalkyl), $-(\text{CH}_2)_{0-4}-\text{N}(\text{R}_{150})-\text{CO}-\text{O}-\text{R}_{150},$
 $-(\text{CH}_2)_{0-4}-\text{N}(\text{R}_{150})-\text{CO}-\text{N}(\text{R}_{150})_2,$ $-(\text{CH}_2)_{0-4}-\text{N}(\text{R}_{150})-\text{CS}-$
5 $\text{N}(\text{R}_{150})_2,$ $-(\text{CH}_2)_{0-4}-\text{N}(\text{R}_{150})-\text{CO}-\text{R}_{105},$ $-(\text{CH}_2)_{0-4}-\text{NR}_{105}\text{R}'_{105},$
 $-(\text{CH}_2)_{0-4}-\text{R}_{140},$ $-(\text{CH}_2)_{0-4}-\text{O}-\text{CO}-\text{(C}_1-\text{C}_6$ alkyl), $-(\text{CH}_2)_{0-4}-\text{O}-$
 $\text{P}(\text{O})-(\text{O}-\text{R}_{110})_2,$ $-(\text{CH}_2)_{0-4}-\text{O}-\text{CO}-\text{N}(\text{R}_{150})_2,$ $-(\text{CH}_2)_{0-4}-\text{O}-\text{CS}-$
 $\text{N}(\text{R}_{150})_2,$ $-(\text{CH}_2)_{0-4}-\text{O}-\text{(R}_{150}),$ $-(\text{CH}_2)_{0-4}-\text{O}-\text{R}_{150}'-\text{COOH},$ $-(\text{CH}_2)_{0-4}-$
 $\text{S}-\text{(R}_{150}),$ $-(\text{CH}_2)_{0-4}-\text{N}(\text{R}_{150})-\text{SO}_2-\text{R}_{105},$ $-(\text{CH}_2)_{0-4}-$
 C_3-C_7 cycloalkyl, (C₂-C₁₀) alkenyl, or (C₂-C₁₀) alkynyl.

10

5. A compound according to claim 4 of the formula I-3-b:



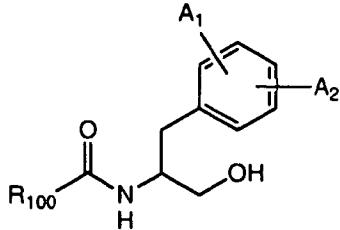
I-3-b

wherein

A₁ and A₂ are independently selected from halogen, C₁-C₄ alkoxy,
15 hydroxy, -NO₂, and C₁-C₄ alkyl optionally substituted with
1, 2, or 3 substituents independently selected from
halogen, OH, SH, NH₂, NH(C₁-C₆ alkyl), N-(C₁-C₆ alkyl)(C₁-C₆
alkyl), C≡N, CF₃.

20

6. A compound according to claim 4 of the formula I-4-b:



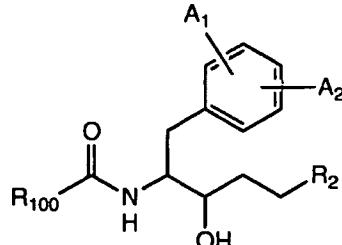
I-4-b

wherein

A₁ and A₂ are independently selected from halogen, C₁-C₄ alkoxy,
hydroxy, -NO₂, and C₁-C₄ alkyl optionally substituted with

1, 2, or 3 substituents independently selected from halogen, OH, SH, NH₂, NH(C₁-C₆ alkyl), N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), C≡N, CF₃.

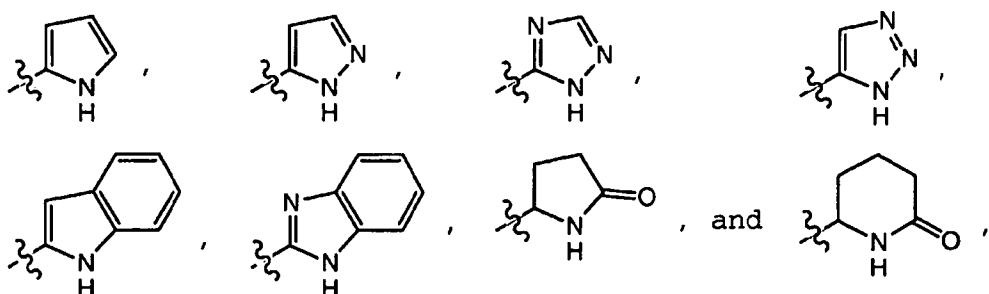
5 7. A compound according to claim 4 of the formula I-5-b:



wherein

A₁ and A₂ are independently selected from halogen, C₁-C₄ alkoxy, hydroxy, -NO₂, and C₁-C₄ alkyl optionally substituted with 10 1, 2, or 3 substituents independently selected from halogen, OH, SH, NH₂, NH(C₁-C₆ alkyl), N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), C≡N, CF₃.

8. A compound according to claim 7 wherein R₂ is 15 selected from the group consisting of:



Where each ring is optionally substituted with 1 or 2 R₁₂₅ groups.

9. A compound according to claim 1 selected from the group consisting of:

N'-(1S)-1-(3,5-difluorobenzyl)-2-hydroxyethyl]-5-methyl-N,N-dipropyl-isophthalamide,

N'-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-pyrrol-2-yl)butyl]-5-methyl-*N,N*-dipropylisophthalamide,

N'-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-pyrazol-5-yl)butyl]-5-methyl-*N,N*-dipropylisophthalamide,

N'-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-1,2,4-triazol-5-yl)butyl]-5-methyl-*N,N*-dipropylisophthalamide,

N'-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-1,2,3-triazol-5-yl)butyl]-5-methyl-*N,N*-dipropylisophthalamide,

N'-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-indol-2-yl)butyl]-5-methyl-*N,N*-dipropylisophthalamide,

N'-[4-(1*H*-benzimidazol-2-yl)-1-(3,5-difluorobenzyl)-2-hydroxybutyl]-5-methyl-*N,N*-dipropylisophthalamide,

N'-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(5-oxopyrrolidin-2-yl)butyl]-5-methyl-*N,N*-dipropylisophthalamide,

N'-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(6-oxopiperidin-2-yl)butyl]-5-methyl-*N,N*-dipropylisophthalamide,

*N*³-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-pyrrol-2-yl)butyl]-*N*¹,*N*¹-dipropylbenzene-1,3,5-tricarboxamide,

*N*³-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-pyrazol-5-yl)butyl]-*N*¹,*N*¹-dipropylbenzene-1,3,5-tricarboxamide,

*N*³-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-1,2,4-triazol-5-yl)butyl]-*N*¹,*N*¹-dipropylbenzene-1,3,5-tricarboxamide,

*N*³-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-1,2,3-triazol-5-yl)butyl]-*N*¹,*N*¹-dipropylbenzene-

1,3,5-tricarboxamide,

N^3 -[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-indol-2-yl)butyl]- N^1,N^1 -dipropylbenzene-1,3,5-tricarboxamide,

N^3 -[4-(1*H*-benzimidazol-2-yl)-1-(3,5-difluorobenzyl)-2-hydroxybutyl]- N^1,N^1 -dipropylbenzene-1,3,5-tricarboxamide,

N^3 -[1-(3,5-difluorobenzyl)-2-hydroxy-4-(5-oxopyrrolidin-2-yl)butyl]- N^1,N^1 -dipropylbenzene-1,3,5-tricarboxamide,

N^3 -[1-(3,5-difluorobenzyl)-2-hydroxy-4-(6-oxopiperidin-2-yl)butyl]- N^1,N^1 -dipropylbenzene-1,3,5-tricarboxamide,

N -[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-pyrrol-2-yl)butyl]-2-(dipropylamino)-6-(1,3-oxazol-2-yl)isonicotinamide,

N -[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-pyrazol-5-yl)butyl]-2-(dipropylamino)-6-(1,3-oxazol-2-yl)isonicotinamide,

N -[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-1,2,4-triazol-5-yl)butyl]-2-(dipropylamino)-6-(1,3-oxazol-2-yl)isonicotinamide,

N -[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-1,2,3-triazol-5-yl)butyl]-2-(dipropylamino)-6-(1,3-oxazol-2-yl)isonicotinamide,

N -[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-indol-2-yl)butyl]-2-(dipropylamino)-6-(1,3-oxazol-2-yl)isonicotinamide,

N -[4-(1*H*-benzimidazol-2-yl)-1-(3,5-difluorobenzyl)-2-hydroxybutyl]-2-(dipropylamino)-6-(1,3-oxazol-2-yl)isonicotinamide,

N -[1-(3,5-difluorobenzyl)-2-hydroxy-4-(5-oxopyrrolidin-2-yl)butyl]-2-(dipropylamino)-6-(1,3-oxazol-2-yl)isonicotinamide,

N -[1-(3,5-difluorobenzyl)-2-hydroxy-4-(6-

oxopiperidin-2-yl)butyl]-2-(dipropylamino)-6-(1,3-oxazol-2-yl)isonicotinamide,

1-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-pyrrol-2-yl)butyl]-5-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoline-7-carboxamide,

1-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-pyrazol-5-yl)butyl]-5-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoline-7-carboxamide,

1-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-1,2,4-triazol-5-yl)butyl]-5-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoline-7-carboxamide,

1-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-1,2,3-triazol-5-yl)butyl]-5-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoline-7-carboxamide,

1-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-indol-2-yl)butyl]-5-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoline-7-carboxamide,

N-[4-(1*H*-benzimidazol-2-yl)-1-(3,5-difluorobenzyl)-2-hydroxybutyl]-1-butyl-5-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoline-7-carboxamide,

1-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(5-oxopyrrolidin-2-yl)butyl]-5-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoline-7-carboxamide,

1-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(6-oxopiperidin-2-yl)butyl]-5-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoline-7-carboxamide,

4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-pyrrol-2-yl)butyl]-8-(1,3-oxazol-2-yl)-3,4-dihydro-2*H*-1,4-benzoxazine-6-carboxamide,

4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-pyrazol-5-yl)butyl]-8-(1,3-oxazol-2-yl)-3,4-dihydro-2*H*-1,4-benzoxazine-6-carboxamide,

4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-1,2,4-triazol-5-yl)butyl]-8-(1,3-oxazol-2-

yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide,
4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-
4-(1H-1,2,3-triazol-5-yl)butyl]-8-(1,3-oxazol-2-
yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide,
4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-
4-(1H-indol-2-yl)butyl]-8-(1,3-oxazol-2-yl)-3,4-
dihydro-2H-1,4-benzoxazine-6-carboxamide,
N-[4-(1H-benzimidazol-2-yl)-1-(3,5-
difluorobenzyl)-2-hydroxybutyl]-4-butyl-8-(1,3-
oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-
carboxamide
4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-
4-(5-oxopyrrolidin-2-yl)butyl]-8-(1,3-oxazol-2-
yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide,
4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-
4-(6-oxopiperidin-2-yl)butyl]-8-(1,3-oxazol-2-yl)-
3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide,
4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-
4-(1H-pyrrol-2-yl)butyl]-8-(1,3-oxazol-2-yl)-3,4-
dihydro-2H-1,4-benzothiazine-6-carboxamide,
4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-
4-(1H-pyrazol-5-yl)butyl]-8-(1,3-oxazol-2-yl)-3,4-
dihydro-2H-1,4-benzothiazine-6-carboxamide,
4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-
4-(1H-1,2,4-triazol-5-yl)butyl]-8-(1,3-oxazol-2-
yl)-3,4-dihydro-2H-1,4-benzothiazine-6-
carboxamide,
4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-
4-(1H-1,2,3-triazol-5-yl)butyl]-8-(1,3-oxazol-2-
yl)-3,4-dihydro-2H-1,4-benzothiazine-6-
carboxamide,
4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-
4-(1H-indol-2-yl)butyl]-8-(1,3-oxazol-2-yl)-3,4-
dihydro-2H-1,4-benzothiazine-6-carboxamide,
N-[4-(1H-benzimidazol-2-yl)-1-(3,5-

difluorobenzyl)-2-hydroxybutyl]-4-butyl-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide,

4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(5-oxopyrrolidin-2-yl)butyl]-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide,

4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(6-oxopiperidin-2-yl)butyl]-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide,

4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1H-pyrrol-2-yl)butyl]-8-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoxaline-6-carboxamide,

4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1H-pyrazol-5-yl)butyl]-8-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoxaline-6-carboxamide,

4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1H-1,2,4-triazol-5-yl)butyl]-8-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoxaline-6-carboxamide,

4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1H-1,2,3-triazol-5-yl)butyl]-8-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoxaline-6-carboxamide,

4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(1H-indol-2-yl)butyl]-8-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoxaline-6-carboxamide,

N-[4-(1H-benzimidazol-2-yl)-1-(3,5-difluorobenzyl)-2-hydroxybutyl]-4-butyl-8-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoxaline-6-carboxamide,

4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(5-oxopyrrolidin-2-yl)butyl]-8-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoxaline-6-carboxamide,

4-butyl-N-[1-(3,5-difluorobenzyl)-2-hydroxy-4-(6-oxopiperidin-2-yl)butyl]-8-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoxaline-6-carboxamide

1-butyl-*N*-(1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-pyrrol-2-yl)butyl)-1*H*-indole-6-carboxamide
1-butyl-*N*-(1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-pyrazol-5-yl)butyl)-1*H*-indole-6-carboxamide,
1-butyl-*N*-(1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-1,2,4-triazol-5-yl)butyl)-1*H*-indole-6-carboxamide,
1-butyl-*N*-(1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-1,2,3-triazol-5-yl)butyl)-1*H*-indole-6-carboxamide,
1-butyl-*N*-(1-(3,5-difluorobenzyl)-2-hydroxy-4-(1*H*-indol-2-yl)butyl)-1*H*-indole-6-carboxamide,
N-(4-(1*H*-benzimidazol-2-yl)-1-(3,5-difluorobenzyl)-2-hydroxybutyl)-1-butyl-1*H*-indole-6-carboxamide,
1-butyl-*N*-(1-(3,5-difluorobenzyl)-2-hydroxy-4-(5-oxopyrrolidin-2-yl)butyl)-1*H*-indole-6-carboxamide,
1-butyl-*N*-(1-(3,5-difluorobenzyl)-2-hydroxy-4-(6-oxopiperidin-2-yl)butyl)-1*H*-indole-6-carboxamide,
1-butyl-*N*-(2-(3,5-difluorophenyl)ethyl)-1*H*-indole-6-carboxamide,
4-butyl-*N*-(2-(3,5-difluorophenyl)ethyl)-8-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoxaline-6-carboxamide,
4-butyl-*N*-(2-(3,5-difluorophenyl)ethyl)-8-(1,3-oxazol-2-yl)-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxamide,
4-butyl-*N*-(2-(3,5-difluorophenyl)ethyl)-8-(1,3-oxazol-2-yl)-3,4-dihydro-2*H*-1,4-benzoxazine-6-carboxamide,
1-butyl-*N*-(2-(3,5-difluorophenyl)ethyl)-5-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoline-7-carboxamide,

N-[2-(3,5-difluorophenyl)ethyl]-2-(dipropylamino)-6-(1,3-oxazol-2-yl)isonicotinamide,
1-butyl-*N*-[1-(3,5-difluorobenzyl)-2-hydroxyethyl]-1*H*-indole-6-carboxamide,
4-butyl-*N*-[1-(3,5-difluorobenzyl)-2-hydroxyethyl]-8-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoxaline-6-carboxamide,
4-butyl-*N*-[1-(3,5-difluorobenzyl)-2-hydroxyethyl]-8-(1,3-oxazol-2-yl)-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxamide,
4-butyl-*N*-[1-(3,5-difluorobenzyl)-2-hydroxyethyl]-8-(1,3-oxazol-2-yl)-3,4-dihydro-2*H*-1,4-benzoxazine-6-carboxamide,
1-butyl-*N*-[1-(3,5-difluorobenzyl)-2-hydroxyethyl]-5-(1,3-oxazol-2-yl)-1,2,3,4-tetrahydroquinoline-7-carboxamide, and
N-[1-(3,5-difluorobenzyl)-2-hydroxyethyl]-2-(dipropylamino)-6-(1,3-oxazol-2-yl)isonicotinamide.

10. A method for the treatment or prevention of Alzheimer's disease, mild cognitive impairment Down's syndrome,
5 Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, cerebral amyloid angiopathy, other degenerative dementias, dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia
10 associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease comprising administration of a therapeutically effective amount of a compound or salt according to Claim 1, to a patient in need thereof.

11. A method of treatment as in claim 10, wherein the patient is a human.

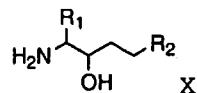
12. A method of treatment according to claim 10, wherein 5 the disease is dementia.

13. The use of a compound or salt according to claim 1 for the manufacture of a medicament.

10 14. The use of a compound or salt according to claim 1 for the manufacture of a medicament for use in the treatment or prevention of Alzheimer's disease, mild cognitive impairment Down's syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, cerebral amyloid angiopathy, 15 other degenerative dementias, dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, or diffuse Lewy body type of Alzheimer's disease.

20

15. A compound of the formula X:



wherein

25 R_1 is $-(\text{CH}_2)_{1-2}-\text{S}(\text{O})_{0-2}-(\text{C}_1-\text{C}_6 \text{ alkyl})$, or

C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, $-\text{OH}$, $=\text{O}$, $-\text{SH}$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, $-\text{C}_1-\text{C}_3$ alkoxy, amino, mono- or dialkylamino, $-\text{N}(\text{R})\text{C}(\text{O})\text{R}'-$, $-\text{OC}(\text{=O})-\text{amino}$ and $-\text{OC}(\text{=O})-\text{mono-}$ or dialkylamino, or

30 C_2-C_6 alkenyl or C_2-C_6 alkynyl, each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, $-\text{OH}$, $-\text{SH}$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, C_1-C_3 alkoxy, amino, and mono- or dialkylamino, or

aryl, heteroaryl, heterocyclyl, aryl-(C₁-C₆)alkyl-, heteroaryl-(C₁-C₆)alkyl-, or heterocyclyl-(C₁-C₆)alkyl-, where the ring portions of each are optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, -OH, -SH, -C≡N, -NO₂, -NR₁₀₅R'₁₀₅, -CO₂R, -N(R)COR', -N(R)SO₂R', -C(=O)-(C₁-C₄) alkyl, -SO₂-amino, -SO₂-monoalkylamino, -SO₂-dialkylamino, -C(=O)-amino, -C(=O)-monoalkylamino, -C(=O)-dialkylamino, -SO₂-(C₁-C₄) alkyl,
C₁-C₆ alkoxy optionally substituted with 1, 2, or 3 groups which are independently selected from halogen,
C₃-C₇ cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, -C₁-C₆ alkyl and mono- or dialkylamino,
C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino and -C₁-C₃ alkyl, and
C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, C₁-C₆ alkyl and mono- or dialkylamino; and the heterocyclyl group is optionally further substituted with oxo;
R and R' independently are hydrogen, C₁-C₁₀ alkyl, C₁-C₁₀ alkylaryl or C₁-C₁₀ alkylheteroaryl;
R₂ is R₁₂₀ or R₁₃₀;
R₁₂₀ is heteroaryl, which is optionally substituted with 1 or 2 R₁₂₅ groups; and
R₁₃₀ is heterocyclyl optionally substituted with 1 or 2 R₁₂₅ groups; and

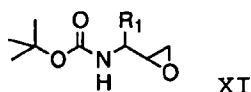
R_{125} at each occurrence is independently halogen, amino, mono- or dialkylamino, -OH, -C≡N, -SO₂-NH₂, -SO₂-NH-C₁-C₆ alkyl, -SO₂-N(C₁-C₆ alkyl)₂, -SO₂-(C₁-C₄ alkyl), -CO-NH₂, -CO-NH-C₁-C₆ alkyl, or -CO-N(C₁-C₆ alkyl)₂, or

5 C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently selected from C₁-C₃ alkyl, halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, and mono- and dialkylamino, or

10 C₁-C₆ alkoxy optionally substituted with one, two or three of halogen.

16. A compound of the formula XI:

15



wherein

R_1 is -(CH₂)₁₋₂-S(O)₀₋₂-(C₁-C₆ alkyl), or

20 C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, =O, -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino, -N(R)C(O)R'-, -OC(=O)-amino and -OC(=O)-mono- or dialkylamino, or

25 C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, and mono- or dialkylamino, or

aryl, heteroaryl, heterocyclyl, aryl-(C₁-C₆)alkyl-, heteroaryl-(C₁-C₆)alkyl-, or heterocyclyl-(C₁-C₆)alkyl-, where the ring portions of each are optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, -OH, -SH, -C≡N, -NO₂, -NR₁₀₅R'₁₀₅, -CO₂R, -N(R)COR', -N(R)SO₂R',

30

-C(=O)-(C₁-C₄) alkyl, -SO₂-amino, -SO₂-monoalkylamino, -SO₂-dialkylamino, -C(=O)-amino, -C(=O)-monoalkylamino, -C(=O)-dialkylamino, -SO₂-(C₁-C₄) alkyl,

5 C₁-C₆ alkoxy optionally substituted with 1, 2, or 3 groups which are independently selected from halogen,

C₃-C₇ cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -

10 OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, -C₁-C₆ alkyl and mono- or dialkylamino,

C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or

15 dialkylamino and -C₁-C₃ alkyl, and

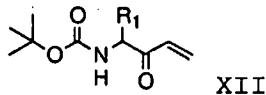
C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, C₁-C₆ alkyl and

20 mono- or dialkylamino; and the heterocyclyl group is optionally further substituted with oxo;

R and R' independently are hydrogen, C₁-C₁₀ alkyl, C₁-C₁₀ alkylaryl or C₁-C₁₀ alkylheteroaryl.

25

17. A compound of the formula XII:



wherein

R₁ is -(CH₂)₁₋₂-S(O)₀₋₂-(C₁-C₆ alkyl), or

30 C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, =O, -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or

dialkylamino, $-\text{N}(\text{R})\text{C}(\text{O})\text{R}'-$, $-\text{OC}(\text{=O})\text{-amino}$ and $-\text{OC}(\text{=O})\text{-mono-}$ or dialkylamino, or

5 $\text{C}_2\text{-C}_6$ alkenyl or $\text{C}_2\text{-C}_6$ alkynyl, each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, $-\text{OH}$, $-\text{SH}$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, $\text{C}_1\text{-C}_3$ alkoxy, amino, and mono- or dialkylamino, or

10 aryl, heteroaryl, heterocyclyl, aryl- $(\text{C}_1\text{-C}_6)$ alkyl-, heteroaryl- $(\text{C}_1\text{-C}_6)$ alkyl-, or heterocyclyl- $(\text{C}_1\text{-C}_6)$ alkyl-, where the ring portions of each are optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, $-\text{OH}$, $-\text{SH}$, $-\text{C}\equiv\text{N}$, $-\text{NO}_2$, $-\text{NR}_{105}\text{R}'_{105}$, $-\text{CO}_2\text{R}$, $-\text{N}(\text{R})\text{COR}'$, $-\text{N}(\text{R})\text{SO}_2\text{R}'$, $-\text{C}(\text{=O})\text{-}(\text{C}_1\text{-C}_4)$ alkyl, $-\text{SO}_2\text{-amino}$, $-\text{SO}_2\text{-monoalkylamino}$, $-\text{SO}_2\text{-dialkylamino}$, $-\text{C}(\text{=O})\text{-amino}$, $-\text{C}(\text{=O})\text{-}$ monoalkylamino, $-\text{C}(\text{=O})\text{-dialkylamino}$, $-\text{SO}_2\text{-}(\text{C}_1\text{-C}_4)$ alkyl,

15 $\text{C}_1\text{-C}_6$ alkoxy optionally substituted with 1, 2, or 3 groups which are independently selected from halogen,

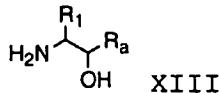
20 $\text{C}_3\text{-C}_7$ cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, $-\text{OH}$, $-\text{SH}$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, $\text{C}_1\text{-C}_3$ alkoxy, amino, $-\text{C}_1\text{-C}_6$ alkyl and mono- or dialkylamino,

25 $\text{C}_1\text{-C}_{10}$ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, $-\text{OH}$, $-\text{SH}$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, $-\text{C}_1\text{-C}_3$ alkoxy, amino, mono- or dialkylamino and $-\text{C}_1\text{-C}_3$ alkyl, and

30 $\text{C}_2\text{-C}_{10}$ alkenyl or $\text{C}_2\text{-C}_{10}$ alkynyl each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, $-\text{OH}$, $-\text{SH}$, $-\text{C}\equiv\text{N}$, $-\text{CF}_3$, $\text{C}_1\text{-C}_3$ alkoxy, amino, $\text{C}_1\text{-C}_6$ alkyl and mono- or dialkylamino; and the heterocyclyl group is optionally further substituted with oxo;

R and R' independently are hydrogen, C₁-C₁₀ alkyl, C₁-C₁₀ alkylaryl or C₁-C₁₀ alkylheteroaryl.

18. A compound of the formula XIII:



wherein

R₁ is -(CH₂)₁₋₂-S(O)₀₋₂-(C₁-C₆ alkyl), or

C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, =O, -SH,
 10 -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino, -N(R)C(O)R'-, -OC(=O)-amino and -OC(=O)-mono- or dialkylamino, or
 C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which is optionally substituted with 1, 2, or 3 groups independently
 15 selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, and mono- or dialkylamino, or
 aryl, heteroaryl, heterocyclyl, aryl-(C₁-C₆)alkyl-, heteroaryl-(C₁-C₆)alkyl-, or heterocyclyl-(C₁-C₆)alkyl-, where the ring portions of each are
 20 optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, -OH, -SH, -C≡N, -NO₂, -NR₁₀₅R'₁₀₅, -CO₂R, -N(R)COR', -N(R)SO₂R',
 -C(=O)-(C₁-C₄) alkyl, -SO₂-amino, -SO₂-monoalkylamino, -SO₂-dialkylamino, -C(=O)-amino, -C(=O)-
 25 monoalkylamino, -C(=O)-dialkylamino, -SO₂-(C₁-C₄) alkyl,
 C₁-C₆ alkoxy optionally substituted with 1, 2, or 3 groups which are independently selected from halogen,
 30 C₃-C₇ cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, -C₁-C₆ alkyl and mono- or dialkylamino,

C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino and -C₁-C₃ alkyl, and

5 C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, C₁-C₆ alkyl and mono- or dialkylamino; and the heterocyclyl

10 group is optionally further substituted with oxo;

R and R' independently are hydrogen, C₁-C₁₀ alkyl, C₁-C₁₀ alkylaryl or C₁-C₁₀ alkylheteroaryl; and

R_a represents hydrogen, hydroxymethyl, or -CH(OH)CH₂CH₂R₂,

15 wherein R₂ is R₁₂₀ or R₁₃₀;

R₁₂₀ is heteroaryl, which is optionally substituted with 1 or 2 R₁₂₅ groups; and

R₁₃₀ is heterocyclyl optionally substituted with 1 or 2 R₁₂₅ groups; and

20 R₁₂₅ at each occurrence is independently halogen, amino, mono- or dialkylamino, -OH, -C≡N, -SO₂-NH₂, -SO₂-NH-C₁-C₆ alkyl, -SO₂-N(C₁-C₆ alkyl)₂, -SO₂-(C₁-C₄ alkyl), -CO-NH₂, -CO-NH-C₁-C₆ alkyl, or -CO-N(C₁-C₆ alkyl)₂, or

C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which

25 is optionally substituted with 1, 2, or 3 groups that are independently selected from C₁-C₃ alkyl, halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, and mono- and dialkylamino, or

C₁-C₆ alkoxy optionally substituted with one, two or three

30 of halogen.

19. A method for the treatment or prevention of Alzheimer's disease, mild cognitive impairment Down's syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-35 Type, cerebral amyloid angiopathy, other degenerative

dementias, dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body 5 type of Alzheimer's disease comprising administration of a therapeutically effective amount of a compound or salt according to any one of Claims 1-18, to a patient in need thereof.

10 20. A method of treatment as in claim 19, wherein the patient is a human.

21. A method of treatment according to claim 19, wherein the disease is dementia.

15 22. The use of a compound or salt according to claim 1 for the manufacture of a medicament.

20 23. The use of a compound or salt according to claim 1 for the manufacture of a medicament for use in the treatment or prevention of Alzheimer's disease, mild cognitive impairment Down's syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, cerebral amyloid angiopathy, other degenerative dementias, dementias of mixed vascular and 25 degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, or diffuse Lewy body type of Alzheimer's disease.

30 24. A method according to claim 19, where the method is for treating Alzheimer's disease.

25. A method of preparing a compound of claim 1.

26. A pharmaceutical composition comprising a compound according to any of claims 1-18.

SEQUENCE LISTING

<110> Gailunas, Andrea
Tucker, John A.
Varghese, John

<120> Substituted Amines for the Treatment of Alzheimer's Disease

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Lys Thr Glu Glu Ile Ser Glu Val Asn Leu Asp Ala Glu Phe
20 25 30

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(71) Applicant (for all designated States except US): ELAN PHARMACEUTICALS, INC. [US/US]; 800 Gateway Boulevard, South San Francisco, Ca 94080 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): GAILUNAS, Andrea [US/US]; 1105 Baywater Avenue, Apartment #1, Burlingame, CA 94010 (US). TUCKER, John, Alan [US/US]; 37 Creekridge Court, San Mateo, CA 94402 (US). JOHN, Varghese [US/US]; 1722 18th Avenue, San Francisco, CA 94122 (US).

(74) Agent: SARUSSI, Steven, J.; McDonnell Boehnen Hulbert & Berghoff, Suite 3200, 300 South Wacker Drive, Chicago, IL 60606 (US).

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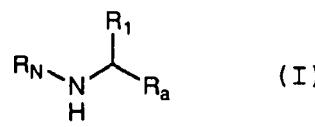
Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
8 April 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2003/027068 A3



(I)

(57) Abstract: Disclosed are compounds of formula (I) which are useful in treating Alzheimer's disease and other similar diseases. These compounds include inhibitors of the beta-secretase enzyme that are useful in the treatment of Alzheimer's disease and other diseases characterized by deposition of A beta peptide in a mammal. The compounds of the invention are useful in pharmaceutical compositions and methods of treatment to reduce A beta peptide formation.

(54) Title: SUBSTITUTED AMINES FOR THE TREATMENT OF NEUROLOGICAL DISORDERS

INTERNATIONAL SEARCH REPORT

PCT/US 02/30231

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 7	C07D233/54	C07D231/12	C07D207/32	C07D249/08	C07D249/04
	C07D209/14	C07D235/14	C07D207/26	C07D211/76	C07D413/14
	C07D417/14	C07D403/12	C07D401/12	C07D209/08	C07D413/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data

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Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/58307 A (NEUROGEN CORP ; YUAN JUN (US); HUTCHISON ALAN J (US); MAYNARD GEORG) 5 October 2000 (2000-10-05) page 3 page 3, last compound page 34 page 37 page 45 page 46 page 48 page 49 claims 15,20,25,35 ----- X WO 88/08424 A (UPJOHN CO) 3 November 1988 (1988-11-03) page 19, line 35 - page 20, line 17 claim 46 ----- -/-	1,5, 10-14, 19-26 1,5,10 -/-

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

9 September 2003

Date of mailing of the international search report

12 02 2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Seitner, I

INTERNATIONAL SEARCH REPORT

PCT/US 02/30231

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *		Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

PCT/US 02/30231

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/78730 A (KAJIGAYA YUKI ; KITO MORIKAZU (JP); OKAJIMA AKIKO (JP); ONO YUKITSU) 28 December 2000 (2000-12-28) -& EP 1 193 259 A (AJINOMOTO KK) 3 April 2002 (2002-04-03) examples 28,29,31,33,38,39 claim 13 -----	1,5, 19-26
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X	WO 00/73283 A (STORMANN THOMAS M ; DELMAR ERIC G (US); MOE SCOTT T (US); SMITH DAR) 7 December 2000 (2000-12-07) figure 2; example 418 examples 413-417 claims 10-12 -----	1,5, 10-14, 19-26
P,X	WO 02/18382 A (AKAHANE ATSUSHI ; ITANI HIROMICHI (JP); OHTAKE HIROAKI (JP); TANAKA) 7 March 2002 (2002-03-07) examples 204,215,269,281 claims 10,11 -----	1,5, 10-14, 19-26
P,X	WO 02/32896 A (SOERENSEN ANDERS ROBERT ; WORSAAE HELLE (DK); HANSEN BO FALCK (DK);) 25 April 2002 (2002-04-25) examples 29,31 claims 41,42 -----	1,5, 10-14, 19-26
P,X	WO 02/34718 A (FARKAS SANDOR ; NAGY JOZSEF (HU); BORZA ISTVAN (HU); DOMANY GYOERGY) 2 May 2002 (2002-05-02) examples 95,96 claim 12 -----	1,5, 10-14, 19-26
P,X	WO 02/059080 A (WILKINSON DOUGLAS ; LIMBURG DAVID (US); VAAL MARK (US); BELYAKOV SE) 1 August 2002 (2002-08-01) example 19 claims 30-37 -----	1,5, 10-14, 19-26
		-/-

INTERNATIONAL SEARCH REPORT

PCT/US 02/30231

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 03/013517 A (CAVICCHIOLI MARCELLO ; SALOM BARBARA (IT); VULPETTI ANNA (IT); PEVA) 20 February 2003 (2003-02-20) claims 2,592,657,680,717,737,838,860,963,986,1029 ,1053 claims 1097,1119,1162,1184,1226,1250,1293,1317,13 59,1380 -----	1,5, 10-14, 19-26
E	WO 03/027076 A (HERREMANS ARNOLDUS H J ; KRUSE CORNELIS G (NL); LANGE JOSEPHUS H M) 3 April 2003 (2003-04-03) example 74 claims 9,10 -----	1,5, 10-14, 19-26
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E	WO 03/053969 A (SANOFI SYNTHELABO ; URBAN-SZABO KATALIN (HU); VARGANE SZEREDI JUDIT) 3 July 2003 (2003-07-03) example 9; table I claim 15 -----	1,5, 10-14, 19-26

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/30231

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 10-12 and 19-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: 1-4, 5, 9-14, 19-26 (all partially) because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-4(all partially); 5(completely); 9-14,19-26(all partially).

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-4,5,9-14,19-26 (all partially)

The initial phase of the search of the first invention revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

For these reasons it appears impossible to execute a meaningful search and/or to issue a complete search report over the whole breadth of the above mentioned claims.

The search and the report for those claims can only be considered complete for:

-the use according to claim 23 of compounds according to formula I-3-b of claim 5,

-compounds per se according to formula I-3-b of claim 5 in which R100 represents 5-alkyl-N,N-dialkylisophthalamide, N1,N1-dialkylbenzene-1,3,5-tricarboxamide, or the pyridine, indole, tetrahydroquinoline, dihydro-2H-1,4-benzoxazine, dihydro-2H-1,4-benzothiazine, and tetrahydroquinoxaline derivatives as depicted in the description on page 21.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-4 (all partially); 5 (completely); 9-14,19-26 (all partially);

Compounds according to formula (I) of claim 1 in which Ra represents hydrogen as well their pharmaceutical use and compositions and the process for their preparation.

2. claims: 1-4 (all partially); 6 (completely); 9-14,19-26 (all partially);

Compounds according to formula (I) of claim 1 in which Ra represents hydroxymethyl as well their pharmaceutical use and compositions and the process for their preparation.

3. claims: 1-4 (all partially); 7-8 (completely); 9-26 (all partially)

Compounds according to formula (I) of claim 1 in which Ra represents $-\text{CH}(\text{OH})\text{CH}_2\text{CH}_2\text{R}_2$ as well their pharmaceutical use and compositions, the process for their preparation, and the intermediates (X), (XI), (XII), (XIII) of claims 15, 16, 17, 18, respectively.

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PCT/US 02/30231

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